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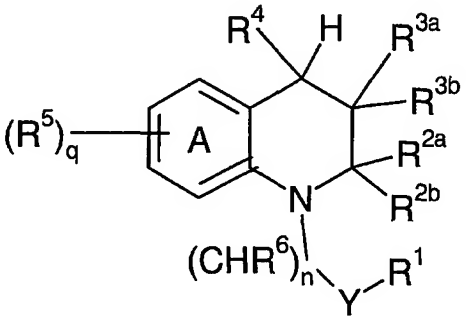
(54) Title: COMPOUNDS AND METHODS FOR TREATING DYSLIPIDEMIA



(I)

(57) Abstract: Compounds of Formula I wherein n, q, Y, R^1, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^4, R^5, and R^6 are as defined herein and their pharmaceutical compositions and methods of use are disclosed.

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COMPOUNDS AND METHODS FOR TREATING DYSLIPIDEMIA

FIELD OF THE INVENTION

The current invention relates to the fields of medicinal organic chemistry, pharmacology, and medicine. Further, the current invention relates to a group of compounds and methods that demonstrate utility for treating pathological states due to dyslipidemia

BACKGROUND OF THE INVENTION

Coronary heart disease (CHD) is one of the major causes of morbidity and mortality worldwide. Despite attempts to modify risk factors such as obesity, smoking, lack of exercise, and treatment of dyslipidemia with dietary modification or drug therapy, CHD remains the most common cause of death in the U.S. Over 50% of all CHD deaths are due to underlying atherosclerotic coronary heart disease.

Dyslipidemia is a major risk factor for CHD. Low plasma levels of high density lipoprotein (HDL) cholesterol with either normal or elevated levels of low density (LDL) cholesterol is a significant risk factor for developing atherosclerosis and associated coronary artery disease in humans. Indeed, several studies on lipoprotein profiles of CHD patients have shown that about 50% of the CHD patients have cholesterol levels that are considered to be in the normal range (<200 mg/dl). Furthermore, these studies found low HDL cholesterol in about 40% of the normo-cholesterolemic CHD patients as compared to the general population reported in the National Health and Nutrition Examination Survey. Since low levels of HDL cholesterol increase the risk of atherosclerosis, methods for elevating plasma HDL cholesterol would be therapeutically beneficial for the treatment of cardiovascular diseases including, but not limited to, atherosclerosis, CHD, stroke, and peripheral vascular disease.

Cholesterol ester transfer protein (CETP) is a 74 KD glycoprotein that facilitates the exchange of cholesterol esters in HDL for triglycerides in triglyceride-rich lipoproteins (A. R. Tall et. al., (1999) 1999 George Lyman Duss Memorial Lecture: Lipid transfer proteins, HDL metabolism and atherogenesis. *Arterio. Thromb. Vasc. Biol.*

20:1185-1188.). The net result of CETP activity is a lowering of HDL cholesterol and an increase in LDL cholesterol. This effect on lipoprotein profile is believed to be pro-atherogenic, especially in subjects whose lipid profile constitutes an increased risk for CHD. Niacin can significantly increase HDL, but has serious toleration issues that reduce compliance. Fibrates and the HMG CoA reductase inhibitors raise HDL cholesterol only modestly (~10-12%). As a result, there is a significant unmet medical need for a well-tolerated agent that can significantly elevate plasma HDL levels, thereby reversing or slowing the progression of atherosclerosis.

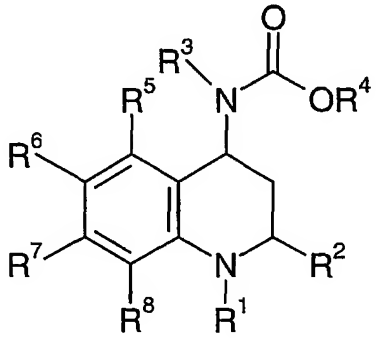
CETP is expressed in multiple tissues and secreted into plasma, where it associates with HDL (X.C. Jiang et al., (1991) Mammalian adipose tissue and muscle are major sources of lipid transfer protein mRNA. *J. Biol. Chem.* 266:4631-4639). Humans and monkeys, which express CETP, have relatively low HDL cholesterol, whereas mice and rats do not express CETP and carry nearly all their cholesterol in HDL. Furthermore, transgenic expression of CETP in mice results in significantly reduced HDL cholesterol levels and developed severe atherosclerosis compared to control mice (K.R. Marotti et. al., (1993) Severe atherosclerosis in transgenic mice expressing simian cholesteryl ester transfer protein. *Nature*: 364, 73-75). Expression of human CETP in Dahl salt-sensitive hypertensive rats led to spontaneous combined hyperlipidemia, coronary heart disease and decreased survival (V.L.M. Herrera et. al., (1999) Spontaneous combined hyperlipidemia, coronary heart disease and decreased survival in Dahl salt-sensitive hypertensive rats transgenic for human cholesteryl ester transfer protein. *Nature Medicine*: 5, 1383-1389).

Antibodies either directly injected into the plasma or generated through vaccine injection can effectively inhibit CETP activity in hamsters and rabbits resulting in elevated HDL cholesterol (C. W. Rittershaus, (1999) Vaccine-induced antibodies inhibit CETP activity in vivo and reduce aortic lesions in a rabbit model of atherosclerosis. Furthermore, antibody neutralization of CETP in rabbits has been shown to be anti-atherogenic (*Arterio. Thromb. Vasc. Biol.* 20, 2106-2112; G.F.Evans et al., (1994) Inhibition of cholesteryl ester transfer protein in normocholesterolemic and hypercholesterolemic hamsters: effects on HDL subspecies, quantity, and apolipoprotein distribution. *J. Lipid Research.* 35, 1634-1645). However, antibody and/or vaccine therapy is not currently a viable option for the treatment of large populations of patients

in need of treatment for dyslipidemia and resultant or associated disease state manifestations.

There have been several reports of small molecule CETP inhibitors. Barrret et al. (J. Am. Chem. Soc., 188, 7863, (1996)) and Kuo et al. (J. Am. Chem. Soc., 117, 10629, (1995)) describe cyclopropan-containing CETP inhibitors. Pietzonka et al. (Biorg. Med. Chem. Lett. 6, 1951 (1996)) describe phosphanate-containing analogs as CETP inhibitors. Coval et al. (Bioorg. Med. Chem. Lett. 5, 605, (1995)) describe Wiedendiol-A and –B related sesquiterpines as CETP inhibitors. Japanese Patent Application No. 10287662-A describes polycyclic, non-amine containing, polyhydroxylic natural compounds possessing CETP inhibition properties. Lee et al. (*J. Antibiotics,* 49, 693-96 (1996)) describe CETP inhibitors derived from an insect fungus. Busch et al. (*Lipids,* 25, 216-220 (1990)) describe cholesteryl acetyl bromide as a CETP inhibitor. Morton and Zillversmit (*J. Lipid Res.,* 35, 836-47 (1982)) describe that p-chloromercuriphenyl sulfonate, p-hydroxymercuribenzoate and ethyl mercurithiosalicylate inhibit CETP. Connolly et al. (*Biochem. Biophys. Res. Comm.* 223, 42-47 (1996)) describe other cysteine modification reagents as CETP inhibitors. Xia et al. Describe 1,3,5-triazines as CETP inhibitors (*Bioorg. Med. Chem. Lett.,* 6, 919-22 (1996)). Bisgaier et al. (*Lipids,* 29, 811-8 (1994) describe 4-phenyl-5-tridecyl-4H-1,2,4-triazole-thiol as a CETP inhibitor. Oomura et al. Disclose non-peptidic tetracyclic and hexacyclic phenols as CETP inhibitors in Japanese Patent Application No. 10287662.

United States patent no. 6,586,448 B1 describes 4-carboxamino-2-substituted-1,2,3,4-tetrahydroquinolines of the following structure:



wherein R^1,R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as defined therein. Similarly, PCT patent applications WO 03/063868A1, WO 00/17164, WO 00/17165, and WO 00/17166,

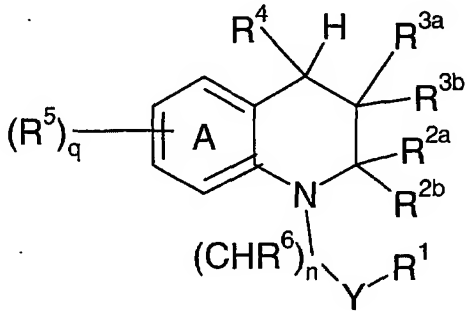
disclose variously, formulations, methods of preparation and methods of use of compounds tetrahydroquinoline compounds generally related to those in U.S patent no. 6,586,448 B1 from which it derives as a divisional application.

European Patent Application No. 818448 by Schmidt et al. describes tetrahydroquinoline derivatives as cholesteryl ester transfer protein inhibitors. European Patent Application No. 818197 by Schmek et al, describe pyridines with fused heterocycles as cholesteryl ester transfer protein inhibitors. Brandes et al. in German Patent Application No. 19627430 describe bicyclic condensed pyridine derivatives as cholesteryl ester transfer protein inhibitors. In US Patent 6,207,671 Schmidt et al. describe substituted pyridine compounds as CETP inhibitors. In PCT Patent Application nos. WO 98/39299, by Müller-Gliemann et al. and WO 03/028727 by Gielen et al. certain quinoline derivatives are described as cholesteryl ester transfer protein inhibitors.

The above disclosures notwithstanding, a great need remains, particularly for affluent western societies for effective compounds useful to treat conditions caused by, associated with, or exacerbated by dyslipidemia.

SUMMARY OF THE INVENTION

The present invention provides a compound of Formula I



I

wherein

n is 0, 1, 2, or 3;

q is 0, 1, 2, 3, or 4;

Y is a bond, C=O, or $S(O)_t$; wherein t is 0, 1, or 2;

R^1 is selected from a group consisting of: hydroxy, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, C_1-C_6

alkylcycloalkyl; C_1-C_6 alkylaryl, heterocyclyl, C_1-C_6 alkylalcohol, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -OC_1-C_6 alkylheterocyclic, -OC_3-C_8 cycloalkyl, -OC_1-C_6 alkylcycloalkyl, -NR^7R^8 and -OC_1-C_6 alkylaryl, -O-heterocyclic, -OC_1-C_6 alkylheterocyclic, C_1-C_6 alkyl-O-C(O)NR^7R^8, C_1-C_6 alkyl-$NR^7C(O)NR^7R^8$, and C_0-C_6 alkyl$COOR^{11}$; provided that R^1 is not hydroxy when Y is $S(O)_t$; and wherein each cycloalkyl, aryl and heterocyclic group is optionally substituted with 1 to 3 groups independently selected from oxo, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkene, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkylalcohol, $CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11},C_0-C_6 alkyl$COOR^{11}$, cyano, C_1-C_6 alkylcycloalkyl, phenyl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylaryl, -OC_1-C_6 alkylheterocyclic, and C_1-C_6 alkylaryl;

R^{2a} and R^{2b} are each independently selected from the group consisting of: hydrogen, hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkene, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, $CONR^{11}R^{12}$, $NR^{11}SO_2R^{12}$, $NR^{11}COR^{12}$, C_0-C_6 alkyl$NR^{11}R^{12}$, C_0-C_6 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, cyano, nitro, C_0-C_6 alkylcycloalkyl, phenyl, C_0-C_6 alkylaryl, heterocyclyl, C_3-C_8 cycloalkyl, and C_1-C_6 haloalkyl; proviced that both R^{2a} and R^{2b} are not simultaneously hydrogen;

R^{3a} and R^{3b} are independently selected from the group consisting of: hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkene, C_2-C_6 alkynyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkyl;

R^4 is a group represented by the formula $-NR^{4a}R^{4b}$;

R^{4a} is a heterocyclic group substituted with 1 to 3 groups independently selected from C_3-C_6 alkyl, C_3-C_6 alkenyl, C_0-C_6 alkylCN, C_3-C_6 alkoxy, C_1-C_6 alkylalcohol, C_3-C_6 haloalkyl, $OC(O)NR^{11}R^{12}$, C_1-C_6 alkyl$NR^{11}R^{12}$ wherein the C_1-C_6 alkyl group (of C_1-C_6 alkyl$NR^{11}R^{12}$) is optionally substituted with -OR^{10} or C(O) OR^{10}, C_0-C_6 alkyl$NR^{11}SO_2R^{12}$, C_0-C_6 alkyl$C(O)NR^{11}R^{12}$, C_0-C_6 alkyl$NR^{11}C(O)R^{12}$, C_0-C_6 alkyl$NR^{11}C(O)OR^{12}$, C_0-C_6 alkyl$NR^{11}CHR^{10}CO_2R^{12}$, C_0-C_6 alkyl$C(O)OR^{11}$, C_0-C_6 alkyl$SO_2NR^{11}R^{12}$, C_0-C_6 alkyl$S(O)_tR^{11}$, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, and C_0-C_6 alkylheterocyclic, wherein the heterocycle of the C_0-C_6 alkylheterocyclic group is optionally substituted with halo, C_1-C_6 alkyl, oxo, -CO_2R^{11} and -$NR^{11}R^{12}$; and

R^{4b} is selected from the group consisting of C_1-C_6 alkylaryl, C_2-C_6 alkenylaryl, C_2-C_6 alkynylaryl, C_1-C_6 alkylheterocyclic, C_2-C_6 alkenylheterocyclic, C_1-C_6 alkylcycloalkyl, and C_1-C_6 alkyl-O-C_1-C_6 alkylaryl, wherein each cycloalkyl, aryl, or

heterocyclic group is optionally substituted with 1-3 groups independently selected from the group consisting of hydroxy, oxo, -SC_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 haloalkyl, halogen, C_1-C_6 alkoxy, aryloxy, C_1-C_6 alkenyloxy, C_1-C_6 haloalkoxyalkyl, C_0-C_6 alkyl$NR^{11}R^{12}$, -OC_1-C_6 alkylaryl, nitro, cyano, C_1-C_6 haloalkylalcohol, and C_1-C_6 alkyl alcohol;

R^5 is selected from a group consisting of: hydrogen, hydroxy, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -C_1-C_6 haloalkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, C_2-C_6 alkenylaryl, C_2-C_6 alkenylheterocyclic, aryl, heterocyclic, cyano, nitro, C_0-C_6 alkylNR^7R^8, C_0-C_6 alkylCOR^7, C_0-C_6 alkylCO_2R^7, C_0-C_6 alkyl$CONR^7R^8$, $CONR^7SO_2R^8$, -$NR^7SO_2R^8$, -NR^7COR^8, -N=CR^7R^8, -O$CONR^7R^8$, S(O)$_t$$R^7$, -$SO_2NR^7R^8$, C_0-C_5CH_2OH, -OC_1-C_6 alkylheterocyclic, and OC_1-C_6 alkylaryl wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclic group or subgroup is optionally substituted with oxo, alkyloxy, aryloxy; and wherein any two R^5 groups may combine to form an optionally substituted 5, 6, or 7-member fused ring with the phenyl ring (A-ring) to which they are attached, wherein the 5, 6, or 7-member fused ring is saturated, partially unsaturated, or fully unsaturated and optionally contains 1, 2, or 3 heteroatoms independently selected from O, N, and S;

R^6 is independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, hydroxy, COR^7, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_1-C_6 alkylNR^7R^8, C_3-C_8 cycloalkyl, heterocyclic, aryl, C_1-C_6 alkyl-O-$C(O)NR^7R^8$, C_1-C_6 alkyl-$NR^7C(O)NR^7R^8$ and C_1-C_6 alkylcycloalkyl;

R^7 and R^8 are each independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -O C_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-aryl, -OC_3-C_8 cycloalkyl, -O-heterocyclic, -NR^7R^8, C_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylheterocyclic, C_1-C_6 alkylheterocyclic, -OC_1-C_6 alkylaryl, C_3-C_8 cycloalkyl, heterocyclic, aryl, and C_1-C_6 alkylaryl, wherein each alkyl, cycloalkyl, heterocyclic or aryl group is optionally substituted with 1-3 groups independently selected from hydroxy, -CN, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and -$NR^{11}R^{12}$, or R^7 and R^8 combine to form a nitrogen containing heterocyclic ring which having 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen and sulfur and

wherein the nitrogen-containing heterocycle is optionally substituted with oxo, or C_1-C_6 alkyl;

R^{10}, R^{11}, and R^{12} are independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclic, aryl, C_1-C_6 alkylaryl, wherein each alkyl, aryl, cycloalkyl, and heterocyclic group is optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkylheterocyclic, and C_1-C_6 haloalkyl, or R^{11} and R^{12} combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen or sulfur and is optionally substituted with oxo, C_1-C_6 alkyl, COR^7, and $-SO_2R^7$;

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

The present invention also provides a method for modulating CETP activity comprising the use of a compound of Formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof, for the treatment, prevention or amelioration of CETP mediated diseases.

The present invention provides a method for treating or preventing dyslipidemia comprising administering a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating or preventing CHD comprising administering a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating and/or preventing atherosclerosis comprising administering a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method for treating and/or preventing diseases related to abnormal CETP activity comprising administering a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of raising the ratio of plasma HDL-cholesterol to plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of raising the level of plasma HDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention provides a method of lowering the level of plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention also provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof, and a carrier.

The present invention also provides a method of treating and/or preventing the pathological sequelae due to low levels of plasma HDL and/or high levels of LDL-cholesterol in a mammal comprising administering an effective dose of a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers, thereof, to a patient in need thereof.

The present invention also relates to the use of a compound of Formula I for the manufacture of a medicament for treating and/or preventing atherosclerosis in a mammal comprising administering an effective dose of a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, mixture of diastereomers, or prodrug thereof, to a patient in need thereof.

The present invention also provides a combination therapy involving a compound of Formula I and one or more other cardio protective agents such as for example, statins, leptin, and/or other LXR, CETP, ABC A1, and/or lipid regulating agents useful for the treatment and/or prevention of atherosclerosis.

DETAILED DESCRIPTION OF THE INVENTION

The current invention provides novel compounds of Formula I useful in modulating CETP activity.

The term "modulation" would include, but not be limited to, up-regulation, down-regulation, inhibition, agonism, antagonism of the CETP receptor as appropriate to achieve HDL raising, or LDL lowering and the resulting biological sequelae from such intervention.

The phrase "diseases" or "diseases related to CETP modulation" or "diseases mediated by CETP activity" refers to pathological states where atherosclerosis and cardiovascular diseases are prone because of dyslipidemia and/or other risk factors and are therefore beneficially affected by down-regulation or modulation of CETP activity. These diseases include but are not limited to hyperlipidemia and its sequelae such as atherosclerosis, CHD, elevated blood pressure, CHF, stroke, hypertension, hypertriglyceremia, diabetes, obesity, inflammatory diseases including but not limited to dermatitis, arthritis, and pain, and diseases of the central nervous system including but not limited to dementia, cognitive disorders such as Alzheimer's disease.

The term "treatment" bears its usual meaning which includes prohibiting, inhibiting, ameliorating, halting, restraining, slowing or reversing the progression, or reducing the severity of a pathological symptom related to or resultant from the modulation of CETP activity, especially as related to raising plasma levels of HDL, or lowering LDL-cholesterol levels or raising the HDL/LDL ratio or controlling atherosclerosis, hyperlipidemia and/or hypercholesterolemia.

Generally, one of skill in the art is aware that valency must be conserved (complete) for all stable molecules. Therefore, the necessary implication that hydrogen atoms are necessary and available to complete valency in all structures including Formula I unless expressly indicated otherwise, is imputed to the general knowledge of one of skill in the art.

General chemical terms used in the description of compounds herein described bear their usual meanings. For example, the term "C_{1-6} alkyl," or "(C_1-C_6) alkyl" or "C_1-C_6 alkyl" refers to a straight or branched aliphatic chain of 1 to 6 carbon atoms including but not limited to methyl, ethyl, propyl, iso-propyl, n-butyl, tert-butyl, pentyl, and hexyl. Unless otherwise stated, the term "alkyl" means C_1-C_6 alkyl. Unless specifically denoted

to the contrary, the carbon atom of alkyl groups are attached to the rest of the referenced molecule. The term "C_0-C_6 alkyl" implies an alkyl group as indicated wherein when the term C_0 applies, the alkyl group is not present, and the remaining groups attach directly to the rest of the referenced molecule.

The term alkenyl and alkynyl, for example, a C_2-C_6 alkenyl group (or a C_2-C_6 alkynyl group) as used herein mean that the respective groups can include 1, 2, or 3 double bonds (or triple bonds). If more than one double or triple bond is present in the group, the double and triple bonds can be conjugated or non-conjugated.

The invention also contemplates that the term C_1-C_6 alkyl or C_2-C_6 alkenyl or similar terms also encompass the specified alkyl or alkenyl or similar group, which may be chiral, regio or steroisomeric. Such chiral or regio or stereoisomeric groups are also objects of the present invention.

The term alkylaryl refers to an alkyl group substituted by an aryl group. For example, C_1-C_6 alkylaryl indicates that an aryl group is attached to a C_1-C_6 alkyl group and that the resulting C_1-C_6 alkylaryl is attached to the rest of the referenced molecule via the alkyl group. A particularly preferred alkylaryl group is benzyl.

The term "substituted phenyl" or "optionally substituted phenyl" refers to a phenyl group having one or more substituents. Preferred substituents are selected from the group consisting of: C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, -$COOR^7$, C_0-C_6 alkylNR^7R^8, nitro, chloro, fluoro, bromo, iodo, C_1-C_6 haloalkyl, C_1-C_6 haloalkoxyalkyl, C_0-C_6 alkylheterocyclic.

The terms "optionally substituted 5-7 member carbocyclic" or "optionally substituted 5-7 member heterocyclic" whether written in the conjunctive or disjunctive style, or in single or in compound sentences, mean a carbocyclic or heterocyclic 5-7 member ring that is optionally substituted with 1-3 groups independently selected from the group consisting of hydroxy, halo (F, Cl, Br or I), C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, aryl, heterocyclic, C_0-C_3 alkylcyano, nitro, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_0-C_6 alkylNR^7R^8, C_0-C_6 alkylCOR^7, C_0-C_6 alkylCO_2R^7, C_0-C_6 alkyl$CONR^7R^8$, $CONR^7SO_2R^8$, -$NR^7SO_2R^8$, NR^7COR^8, -$N{=}CR^7R^8$, $OCONR^7R^8$, -$S(O)_{0\text{-}2}R^7$, -$SO_2NR^7R^8$, C_0-C_5CH_2OH, -OC_1-C_6 alkylheterocyclic, and -OC_1-C_6 alkylaryl.

The term "optionally substituted" in general means that the subject group may be substituted, where possible, with 1-3 groups independently selected from the group consisting of: hydroxy, halogen, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, aryl, heterocyclic, C_0-C_3 alkylcyano, nitro, C_1-C_6 alkyl, C_2-C_6 alkenyl C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_0-C_6 alkylNR^7R^8, C_0-C_6 alkylCOR^7, C_0-C_6 alkylCO_2R^7, C_0-C_6 alkyl$CONR^7R^8$, $CONR^7SO_2R^8$, -$NR^7SO_2R^8$, -NR^7COR^8, -$N{=}CR^7R^8$, -$OCONR^7R^8$, -$S(O)_{0\text{-}2}R^7$, -$SO_2NR^7R^8$, C_0-C_5CH_2OH, -OC_1-C_6 alkylheterocyclic, and -OC_1-C_6 alkylaryl. Where an optionally substituted group is claimed or disclosed, it should be noticed that both the substituted and unsubstituted versions of the subject group are within the purview of the invention unless otherwise indicated.

The term "aryl" refers to a substituted or unsubstituted aromatic or heteroaromatic, or heterocyclic radical. Illustrative aryl groups include but is not limited to napthyl, quinolyl, tetrahydroquinolyl, indazolyl, pyrimidinyl, triazinyl, pyrazine, pyridazinyl, piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, pyranyl, tetrazolyl, imidazolyl, 1,2,3-trazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazopyridine, benzimidazolyl, triazolone-yl, imidazolone-yl, imidazolidinone-yl, 2-furyl, 3-furyl, 2-thienyl 3- thienyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-naphthyl, 2-naphthyl, 2-benzofuryl, 3-benzofuryl, 4-benzofuryl, 5-benzofuryl, 6-benzofuryl, 7-benzofuryl, 2-benzothieny, 3-benzothienyl, 4-benzothienyl, 5-benzothienyl, 6-benzothienyl, 7-benzothienyl, 1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, tetrazole , imidazole, isoxazole, pyrazole, 7-indolyl, and isomers thereof. As used herein the term aryl also encompasses the benzyl group.

The term "carbocycle" as used herein refers to a cyclic group having only carbon and appropriate number of hydrogen atoms. The term encompasses groups such as cycloalkyl, cycloalkene, cycloalkylene, naphthyl, phenyl and the like.

The term "heterocycle", "heterocyclyl", or "heterocyclic" refers to a 5, 6 or 7 member ring, which may be saturated, partially unsaturated or aromatic mono-cyclic or part of a fused bicyclic ring, and can contain 1-5 heteroatoms selected from N, S, or O, and can optionally be substituted at the ring carbon or nitrogen atom(s) unless otherwise specified. Preferred heterocyclic groups include pyrolidinyl, piperidinyl,

hexamethyleneimmino, morpholino, thiomorpholino, benzthiophene, indolyl, quinolyl, isoquinolyl, tetrazolyl, and pyridinyl. As a corollary, the term "alkylheterocyclic" or "alkylheterocycle" is understood to mean that the alkyl group is attached to the heterocycle and the point of attachment to the rest of the referenced molecule is the alkyl group.

The term "haloalkyl" as used herein refers to an alkyl (as noted above) substituted with one or more halo atoms selected from F, Br, Cl, and I.

The term "haloalkoxyalkyl" as used herein include for example trifluoromethoxy, pentafluoroethoxy, trifluoroethoxy (OCH_2CF_3) and the like.

The term "Prodrugs" describes derivatives of the compounds of the invention that have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention, which are pharmaceutically active, in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives, such as, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic esters (e.g., methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl) or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. Other preferred esters include morpholinoethyloxy, diethylglycolamide and diethylaminocarbonylmethoxy. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters.

As used herein, the term "protecting group" refers to a group useful for masking reactive sites in a molecule to enhance the reactivity of another group or allow reaction at another desired site or sites following which the protecting group may be removed. Protecting groups are usually used to protect or mask groups including but not limited to -OH, -NH, and –COOH. Suitable protecting groups are known to one of skill in the art and are described in Protecting groups in Organic Synthesis, 3rd edition, Greene, T. W.; Wuts, P.G.M. Eds., John Wiley and Sons, New York, 1999.

As used herein, the term "solvate" refers to a crystal (or crystals) of a compound of the invention formed to include a stoichiometric or non-stoichiometric amount of the compound of Formula I and a solvent molecule. Typical solvating solvents include for example, water, methanol, ethanol, acetone and dimethylformamide. When the solvent is water, the term hydrate for a stoichiometric or non-stoichiometric amount of compound and water (or hemi-hydrate for half the stoichiometric amount of water) may optionally be used.

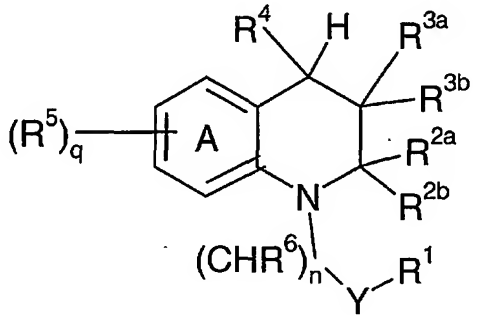
In those instances where a compound of the invention possesses acidic or basic functional groups, various salts may be formed which are more water soluble and/or more physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion-exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base or acid addition salts of compounds of the present invention. Base addition salts include for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, hydrobromide, camsylate, carbonate, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrochloride, hydroxynaphthoate, hydroiodide, isothionate, lactate, lactobionate, laureate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate. Preferred salts for the purpose of the invention include the hydrochloride salt, the hydrobromide salt, the bisulfate salt, the methane sulfonic acid salt, the *p*-toluenesulfonic acid salt, bitartrate, the acetate and the citrate salt.

A compound of the invention as illustrated by Formula I may occur as any one of its positional isomers, stereochemical isomers or regio-isomers, all of which are within the scope of the present invention of the invention. Certain compounds of the invention may possess one or more chiral centers, and thus, may exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group, there exist the possibility of cis and trans isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of enantiomers or cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereo-specific reactions with starting materials that contain the asymmetric centers and are already resolved. Alternatively desired stereoisomers may be prepared by methods that lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound i.e. a chiral resolving agent. This changes the racemic form into a mixture of stereoisomers and diastereomers, because they have different melting points, different boiling points, and different solubilities and can be separated by conventional means, such as crystallization.

Preferred Embodiments of the Invention

Reference will now be made to preferred compounds of the present invention, which are illustrated by Formula 1



Preferred n, m, p, and q

Preferably n is 0, or 1. More preferably, n is 0.

Preferably, q is 0, 1 or 2. More preferably q is 1 or 2. Most preferably, q is 1.

Preferably Y is a bond or C(O);

Preferred R^1

A preferred R^1 group is selected from the group consisting of: hydroxy, -Oaryl, $-OC_1$-C_6 haloalkyl, $-OC_1$-C_6 alkylcycloalkyl, $-OC_3$-C_8 cycloalkyl , $-OC_1$-C_6 alkylcycloalkylNR^7R^8, $-OC_1$-C_6 alkyl, $-OC_0$-C_6 alkylaryl, $-OC_1$-C_6alkylcyano, $-OC_1$-C_6 alkylCO_2R^{11}, $-OC_3$-C_8 cycloalkylCO_2R^{11}, $-OC_1$-C_6alkylhydroxy, $-OC_1$-C_6 alkylNR^7R^8 and $-OC_0$-C_6 alkylheterocyclic; provided that R^1 is not -OH when Y is $-S(O)_t$; and wherein each alkyl, cycloalkyl, aryl, or heterocyclic is optionally substituted with 1 or 2 groups selected from halogen, C_0-C_3 alkylalcohol, C_0-C_3 alkylamine, C_0-C_3 alkylCOOH, C_0-C_3 alkyl$CONH_2$, C_0-C_3alkylcyano, and C_0-C_3 alkyl$C(O)OC_1$-C_3 alkyl.

More preferred an R^1 is selected from: hydroxy, $-OC_1$-C_6 alkyl, $-OC_0$-C_6 alkylaryl, $-OC_1$-C_6 alkylcycloalkyl, $-OC_1$-C_6alkylcyano, $-OC_0$-C_6 alkylheterocyclic, $-OC_1$-C_6 alkylhydroxy, $-OC_1$-C_6 alkylNR^7R^8, $-OC_1$-C_6alkyl$CO_2R^{11}$and $-OC_0$-C_6 alkylcycloalkylNR^7R^8, provided that R^1 is not -OH when Y is $-S(O)_t$, and wherein each alkyl, cycloalkyl, aryl, or heterocyclic is optionally substituted with 1 or 2 groups independently selected from halogen, C_0-C_3 alkylalcohol, C_0-C_3 alkylamine, and C_0-C_3 alkylCOOH, C_0-C_3alkyl$CONH_2$, C_0-C_3alkylcyano, and C_0-C_3 alkyl$C(O)OC_1$-C_3 alkyl. Most preferred R^1 is selected from a by $-OC_1$-C_6 alkyl.

Preferred R^{2a} and R^{2b}

A preferred R^{2a} and R^{2b} groups are independently selected from the group consisting of: hydrogen, C_1-C_6 haloalkyl, C_1-C_6 alkyl, C_1-C_6 alkylcycloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylaryl, and C_0-C_6 alkylNR^7R^8, provided that R^{2a} and R^{2b} are not simultaneously hydrogen.

More preferred R^{2a} or R^{2b} are independently selected from: C_1-C_6 alkylcycloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkyl, and C_1-C_6 alkylaryl.

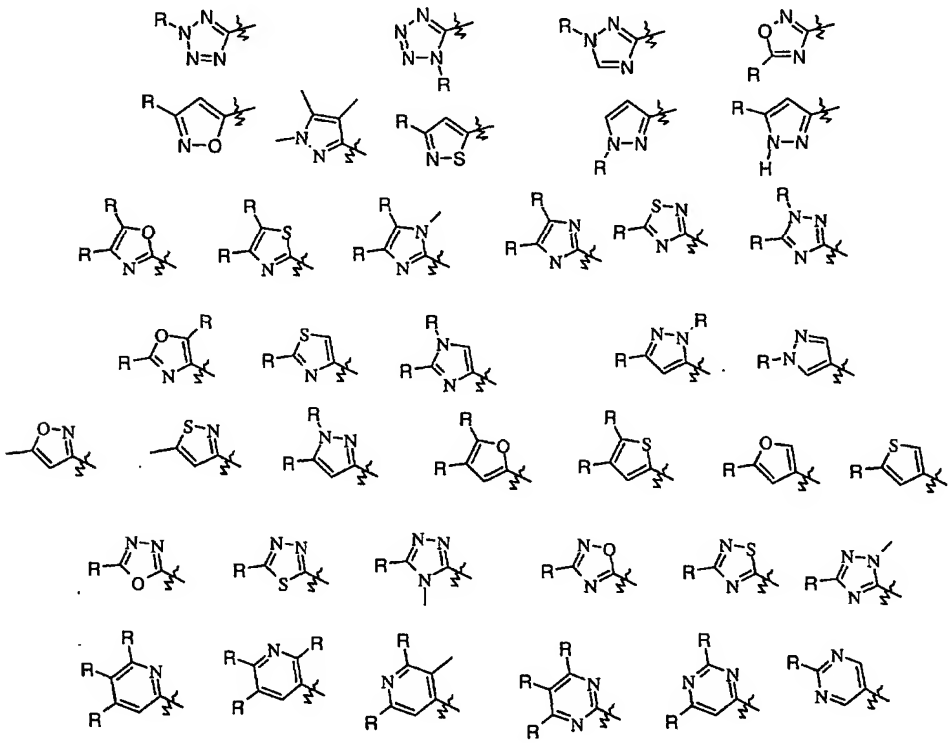
Preferred R^3 Groups

Preferred R^{3a} and R^{3b} groups are independently selected from the group consisting of: hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, and C_2-C_6 alkynyl. More preferably, R^{3a} and R^{3b} are each independently selected from hydrogen and C_1-C_6 alkyl.

Preferred R^4 Groups

Preferred R^4 is $NR^{4a}R^{4b}$

Where preferably R^{4a} is selected from the group consisting of:



wherein, the R groups are independently selected from the group consisting of: C_3-C_6 alkyl, C_1-C_6 alkylalcohol, C_3-C_6 alkoxy, C_0-C_6 alkylcycloalkyl, C_0-C_6 alkylheterocyclic, C_1-C_6 alkylCN, C_3-C_6 haloalkyl, C_0-C_6 alkyl$NR^{11}R^{12}$ wherein the C_1-C_6 alkyl group (of C_1-C_6 alkyl$NR^{11}R^{12}$) is optionally substituted with $-OR^{10}$ or $C(O)\ OR^{10}$, C_1-C_6 alkyl$C(O)NR^{11}R^{12}$, and C_1-C_6 alkyl$C(O)OR^{11}$ provided that the R groups are not hydrogen, methyl, or ethyl. The R^{11} and R^{12} groups are as described below. More preferable the R groups are independently selected from the group consisting of: C_3-C_6

alkyl, C_2-C_6 alkylNH$_2$, C_2-C_6 alkylalcohol, C_1-C_6 alkylcyano, C_1-C_6 alkylC(O)NH$_2$, again provided that the R groups are not hydrogen, methyl or ethyl.

Preferably, R^{4b} is selected from: C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, wherein the heterocyclic and aryl groups are optionally substituted with 1-3 groups selected from the group consisting of: hydroxy, oxo, cyano, -SC_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 haloalkyl, halogen, and -OC_1-C_6 alkyl. More preferably, R^{4b} is benzyl mono or disubstituted with a C_1-C_6 haloalkyl, halogen and C_1-C_3 alkyl. Most preferred for R^{4b} is 3,5-bistrifluorobenzyl.

Preferred R^5 groups

R^5 is preferably selected from a group consisting of hydrogen, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, -OC_1-C_6 alkyl, -Oaryl, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -$CH_2NR^7R^8$, -NH_2, -N(C_1-C_4 alkyl)$_2$, -CN, and -NO_2. Also preferred are any two R^5 groups which combine to form an optionally substituted 5, 6, or 7-member fused ring with the phenyl ring to which they are attached, wherein the 5, 6, or 7-member ring is saturated, partially unsaturated, or fully unsaturated and optionally contains 1, 2, or 3 heteroatoms independently selected from O, N, and S. Optional substituents for the 5, 6 or 7-member fused ring discussed above include preferably, halo, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, $CH_2NR^7R^8$, -NH_2, -N(C_1-C_4 alkyl)$_2$, -CN, and -NO_2.

Preferred R^6 groups

R^6 is at each occurrence independently selected preferably from a group consisting of: hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylhydroxy, phenyl, and C_1-C_6 alkoxy.

Preferred R^7 and R^8 groups

Preferred R^7 and R^8 are independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkylaryl, and C_1-C_6 alkylheterocyclic, wherein each aryl group is optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl, halo, and C_1-C_6 haloalkyl.

Preferred R^{10}, R^{11} and R^{12} groups

Preferred R^{10}, R^{11} and R^{12} are independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkylaryl, and C_1-C_6 alkylheterocyclic, wherein each alkyl and aryl group is optionally substituted with 1-3 groups independently selected from C_1-C_6 alkyl, halo, and C_1-C_6 haloalkyl.

Particularly preferred compounds of the invention are selected from the group consisting of: (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyanomethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-methoxycarbonylmethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-carboxymethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-isopropyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-isobutyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-butyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-*tert*-butyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-hydroxy-ethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(3-hydroxy-propyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-chloro-ethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-carbamoylmethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-dimethylcarbamoylmethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-2-{5-[(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amino]-tetrazol-2-yl}-ethanol,

(2R-4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-dimethylamino-ethyl)-2H-tetrazol-5-yl]-amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-cyano-ethyl)-2H-tetrazol-5-yl]-amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[[2-(3-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-propyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl]-amino}-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-methoxy-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-piperidin-4-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-[[2-(2-Aziridin-1-yl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-pyrrolidin-1-yl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3R-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3R-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3S-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3S-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-piperidin-4-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-[(2-Azetidin-3-yl-2H-tetrazol-5-yl)-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3R-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3R-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3S-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3S-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

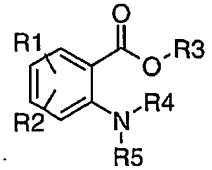
(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester methanesulfonic acid salt and pharmaceutically acceptable salts solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

The geometric isomers associated with the double bonds and the optical isomers associated with asymmetric carbon atoms of compounds of Formula I are also contemplated to be within the scope of the current invention as useful for the treatment of diseases related to CETP modulation.

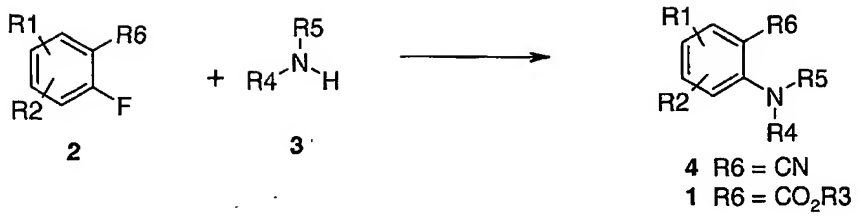
Synthesis of Compounds of the Invention

The compounds of the instant invention can be synthesized as exemplified in the following Schemes, Examples, and Procedures. Anthranilate intermediates of Formula 1 can be chemically prepared, for example, by following the synthetic routes set forth in the Schemes below. However, the following discussion is not intended to limit the scope of the present invention in any way because one of skill in the art is able to extrapolate without undue experimentation from the schemes and examples herein to other specific compounds within the scope of the invention. Many of the reagents and starting materials can be readily obtained from commercial suppliers or are readily available to one of ordinary skill in the art. Other necessary reagents and starting materials may be made by procedures which are selected from standard techniques of organic and heterocyclic chemistry, techniques which are analogous to the syntheses of known similar reagents or starting materials, and the procedures described in the preparations and examples below, including any novel procedures. This includes, but is not limited to, esterification of a carboxylic acid, hydrolysis of a nitrile to a carboxylic acid, and subsequent esterification. The R, R1, R2, R3, R4, R5, R6, etc, designations used within immediately following section are for the purpose of illustrating the various methods of synthesizing compounds of the invention and/or illustrating variability of substituents at the pendent position and are not necessarily synonymous in scope or meaning with similar groups used in the generic structure for compounds of Formula I. However, groups in final compounds of the schemes occupying similar positions are co-extensive in scope and meaning compared to groups occupying similar positions as defined for the generic structure of compounds of Formula I.

Intermediate Preparation Scheme 1

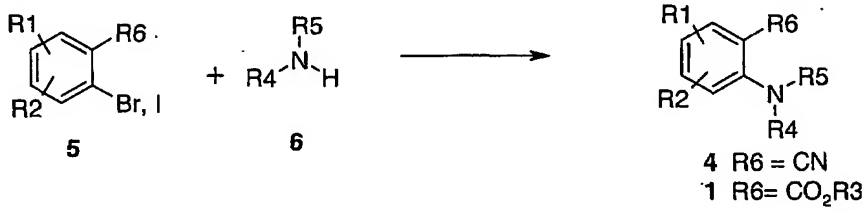


1



In intermediate preparation scheme 1, the nucleophilic aromatic substitution occurs by methods known in the art, (Wells, K. M. et al. Tetrahedron Letters, 1996, 37(36), 6439-6442). The appropriately substituted amine is dissolved in a suitable solvent, such as DMF or DMSO, with a base, such as cesium carbonate, and the appropriately substituted benzonitrile or fluoro benzoate (R6 = CN or CO_2R3). The reaction proceeds at 0°C to elevated temperatures (up to or about 150 °C) in anywhere from ten minutes to several days depending on the stability of the starting materials and/or reaction conditions. The product of structure **4** (R6 = CN) or **1** (R6 = CO_2R3) can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

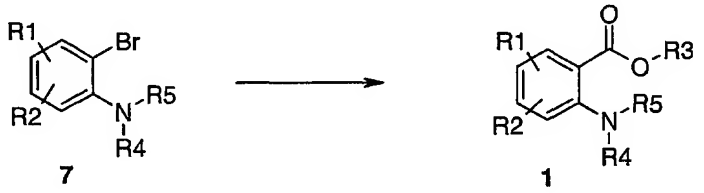
Intermediate Preparation Scheme 2



In intermediate preparation scheme 2, the N-aryl coupling occurs by methods known in the art, (Hartwig, J. F. et al. Angew. Chem., Int. Ed. Engl. 1998, *37*, 2046-2067). The appropriately substituted amine is dissolved in a suitable solvent, such as DMF, with a base, such as cesium carbonate or sodium *tert*-butoxide, the appropriately substituted benzonitrile or halogenated benzoate (R6 = CN or CO_2R3), and a suitable catalyst complex, such as palladium acetate and diphenyl phospino ferrocene. The reaction proceeds at 0°C to elevated temperatures in anywhere from ten minutes to several days depending on the stability of the starting materials. The product of structure

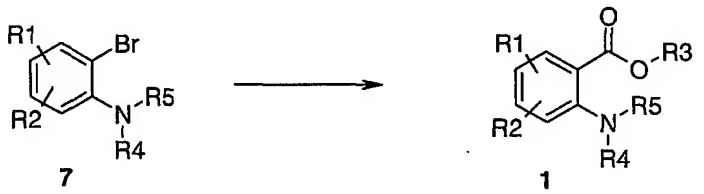
4 (R6 = CN) or **1** (R6 = CO_2R3) can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

Intermediate Preparation Scheme 3



In intermediate preparation scheme 3, the carbonylation occurs by methods known in the art, (Heck, *Palladium Reagents in Organic Synthesis;* Academic Press: New York, 1985, p. 348-358). The appropriately substituted aryl bromide is dissolved in a suitable solvent, such as DMF, with a base, such as cesium carbonate or sodium *tert*-butoxide, a suitable catalyst complex such as palladium acetate and diphenyl phospino ferrocene, an appropriate alcohol (R3-OH) and saturated with carbon monoxide. The reaction proceeds at 0°C to elevated temperatures (up to or about 150 °C) in anywhere from ten minutes to several days depending on the stability of the starting materials and/or reaction conditions. The product of structure **1** may then be isolated by a standard aqueous workup, optionally followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

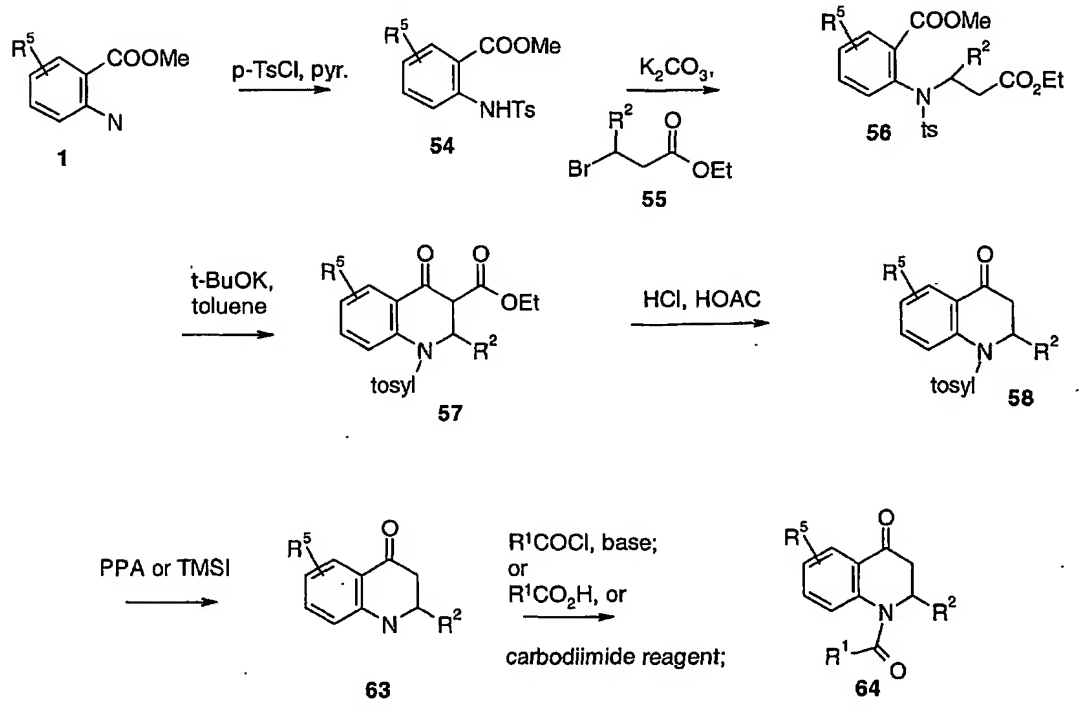
Intermediate Preparation Scheme 4



In intermediate preparation scheme 4, the aromatic carboxylation occurs by methods known in the art, (Boger, D. L. et al, Journal of Organic Chemistry, 1994, 59(17), 4943-4949, Volpin et al, *Organomet. Reactions*, 1975, *5*, 313-386). The

appropriately substituted aryl bromide is dissolved in a suitable solvent, such as diethyl ether or tetrahydrofuran, with an alkyllithium, such as n-butyl lithium or *tert*- butyl lithium or magnesium turnings. The resulting anion is quenched with a suitable carbon dioxide source, such as dry ice, or dimethyl carbonate. The reaction proceeds at about -78°C to about room temperature in anywhere from about five minutes to several hours depending on the stability of the starting materials. The product of structure **1** can then be isolated by a standard aqueous workup, followed by normal phase chromatographic methods or recrystallization techniques commonly employed in the art.

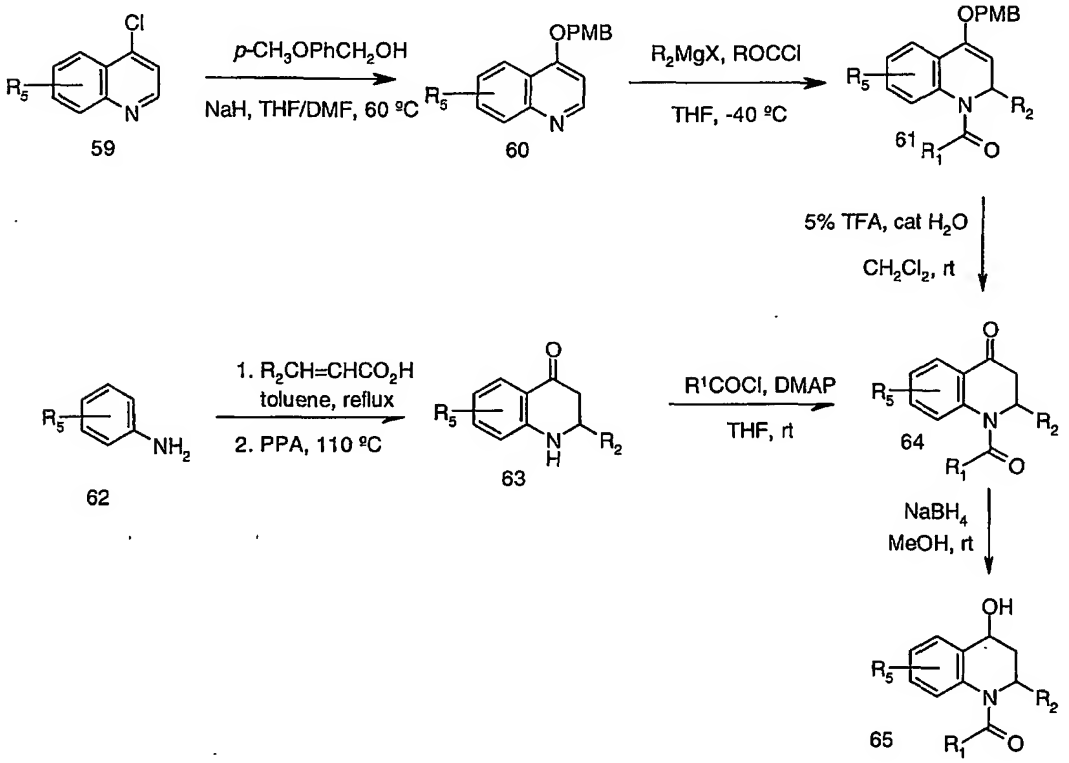
Intermediate Preparation Scheme 5



Synthetic scheme 5 shows preparation of compounds of Formula I. For example, substituted arylamino esters **1** that are either commercially available or prepared as set forth in the literature or in Schemes 1 to 4 can be protected with tosyl chloride, isopropyl chloroformate, or other suitable protecting group to provide **54**. The compound **54** may, in turn, be alkylated with appropriately substituted, or unsubstituted 3-bromoethylesters **55** thus affording **56**. Dieckmann condensation-cyclization of intermediate **56** yields N-

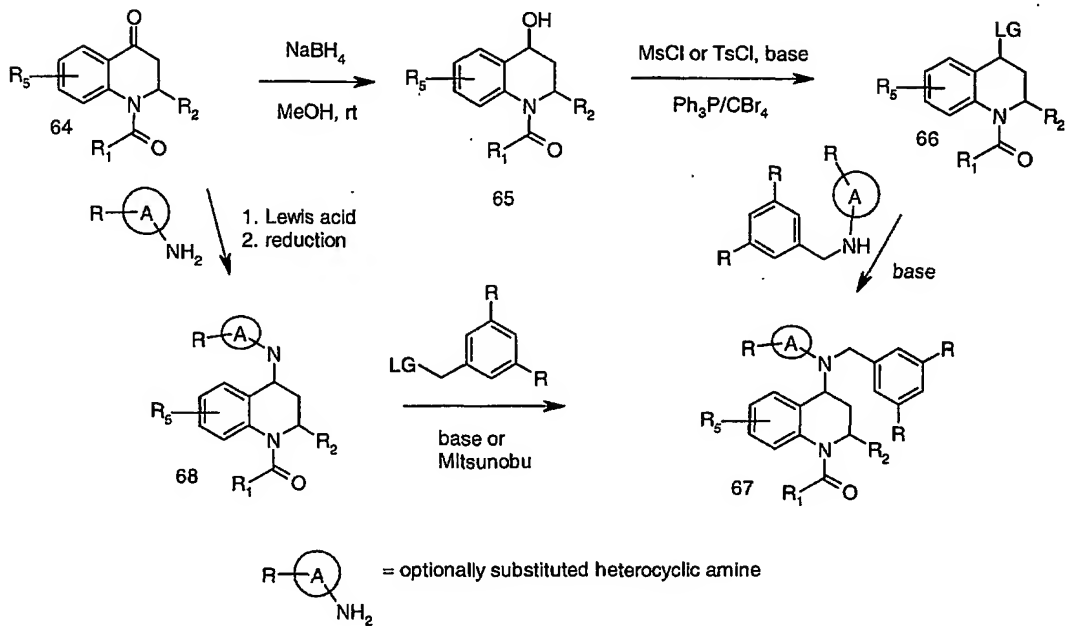
protected tetrahydroquinoline **57**, which is subjected to acid hydrolysis and decarboxylation to afford ketone derivatives **58**. Removal of the protecting group, if necessary, with acid (e.g. PPA (polyphosphoric acid)), TMSI (trimethylsilyliodide), or HCl provides the intermediate **63**. N-acylation of **63** by treatment with an appropriately substituted aryl or alkyl chloroformate in the presence of an organic base such as pyridine affords carbamates of structure **64**. Alternatively, treatment of **63** with an acid chloride or an appropriate activated ester, affords compounds of formula **64**.

Intermediate Preparation Scheme 6



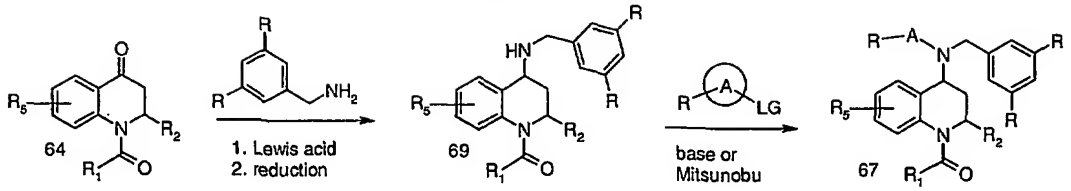
Alternatively compound **64** can be obtained as is shown in Scheme 6, by addition of a Grignard reagent to compound **60** followed by hydrolysis in acid media. Or, Michael addition of aniline derivatives **62** to α, β-unsaturated carboxylic acid or ester, followed by cyclization in acid media, can afford compound **63**. The intermediate tetrahydroquinoline-4-ones **64** may be reduced with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran or methanol, to achieve the benzylic alcohol **65** as shown in Scheme 6.

Scheme 7



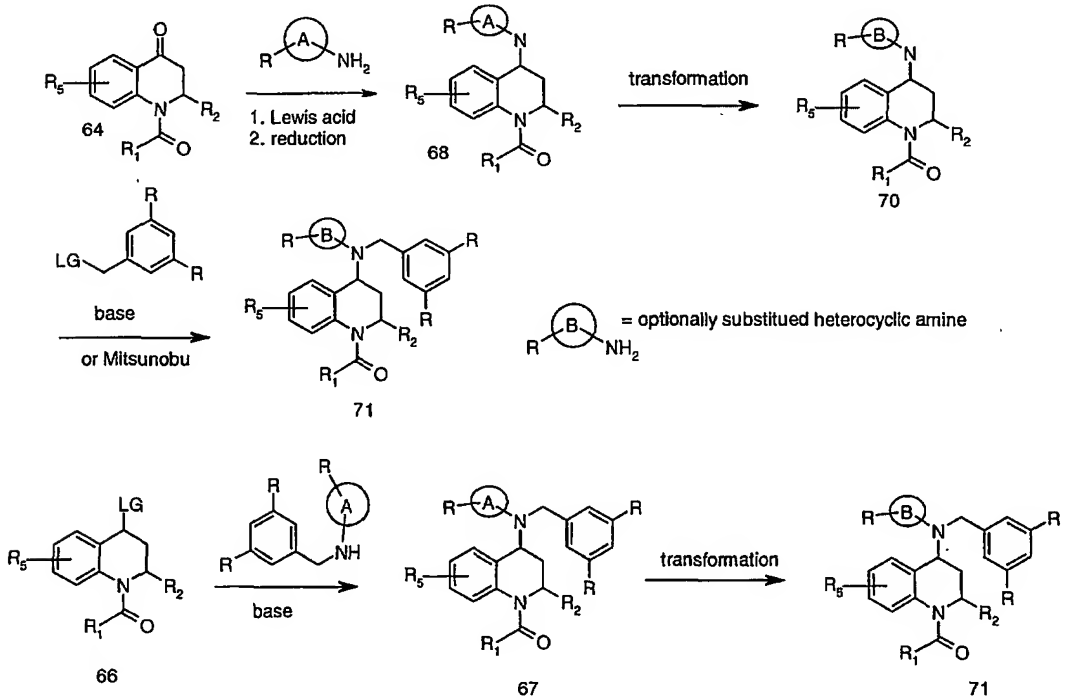
Compounds of Formula I may be prepared as shown in Schemes 7 and 8, in which reductive amination chemistry is utilized. Formation of a Schiff base of tetrahydroquinoline-4-ones **64** with a heterocyclic amine is followed by treatment with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran or methanol, to achieve the heterocyclic amine adducts. Further elaboration by reaction with an activated benzylic reagent in the presence of base or the use of a Mitsunobu-type displacement reaction affords the corresponding product, a compound of the invention. Alternatively, the tetrahydroquinoline-4-ones (**64**) may be reduced to the corresponding carbinol intermediate with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran or methanol. These adducts may be converted directly to provide disubstituted amine products using the Mitsunobu protocol, or initially converted to activated templates such as a mesylate, tosylate or bromide and displaced with the heterocyclic-substituted benzylamine to achieve trisubstituted amine products as shown in Scheme 7. A preferred group of potential heterocyclic R-A substituents has been disclosed supra.

Scheme 8



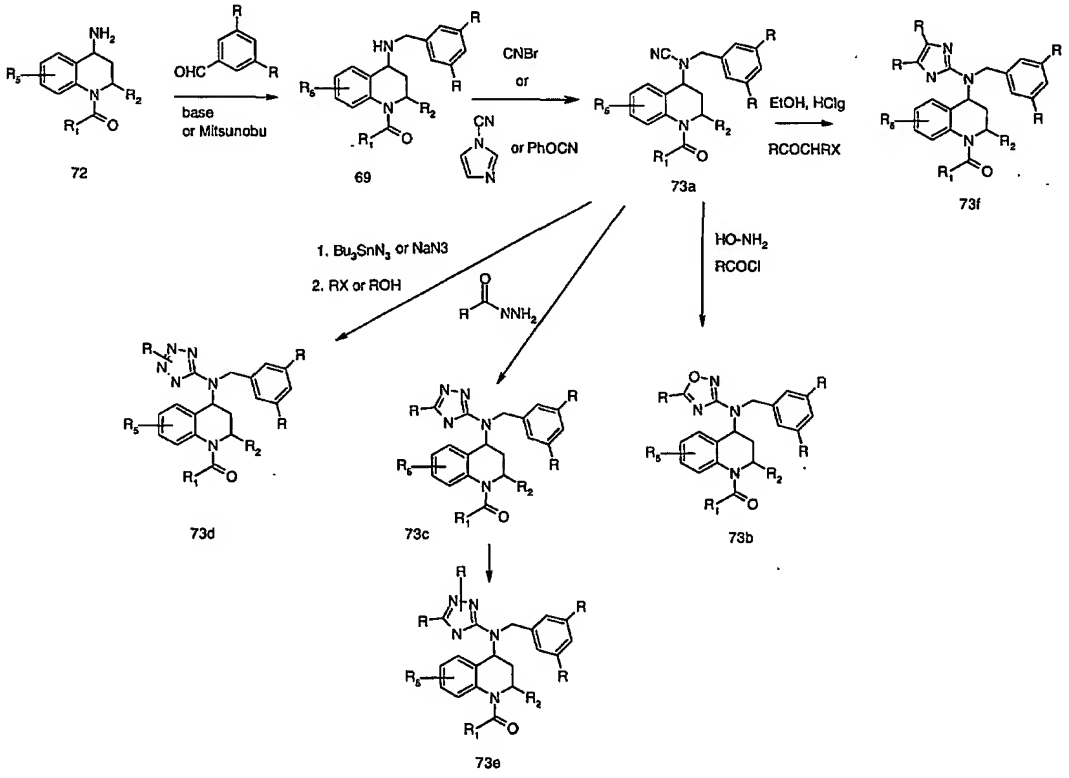
A reverse procedure for forming the disubstituted amine is shown in Scheme 8. Formation of a Schiff base of a tetrahydroquinoline-4-one (**64**) with a benzylic amine is followed by treatment with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran or methanol, to achieve the disubstitued benzylic amine adduct **69**. Further elaboration by reaction with an activated heterocylic reagent in the presence of base (or alternatively, Schiff base formation with a heteroaromatic aldehyde followed by reduction) provides a secondary route to disubstituted amine products **67**.

Scheme 9



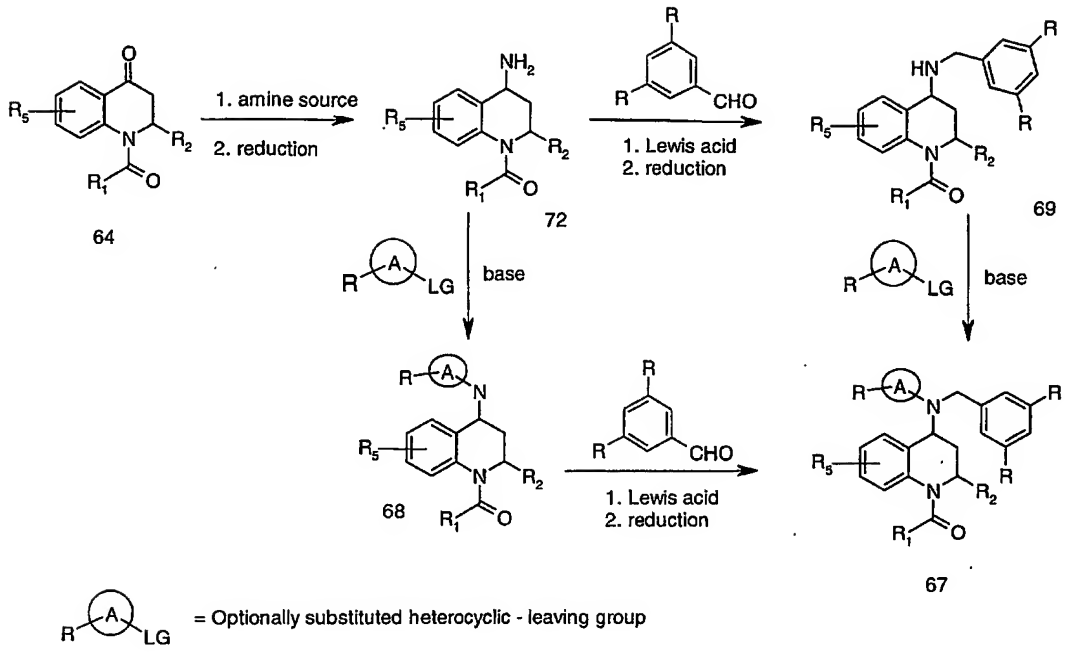
Compounds of Formula I may also be prepared by transformation of pendant functionality as shown in Scheme 9. Scheme 9 shows that disubstituted amine products such as **68** in which the moiety R-A corresponds to reactive functionality such as cyano, carboxylate, or like group may be transformed into heterocyclic moieties such as **71** in intermediate stages of synthesis or at the end of the synthetic preparation. Also, the order of N-substitution may be reversed as shown above. Procedures for transforming pendant functionalities wherein R-A corresponds to a reactive functionality are known to one of skill in the art and may be found in general organic and/or heterocyclic chemistry reference text such as but not limited to *Comprehensive Organic Transformations*, 2nd, ed., by Richard Larock, Wiley-VCH, Publishers, New York.

Scheme 9a



Scheme 9a shows a few examples of transformation reactions to illustrate inter-conversion of functionalities as means of preparing compounds of the invention. Detailed procedures are disclosed in the Examples, known to one of skill in the art, or are readily available from reference sources by one of skill in the art.

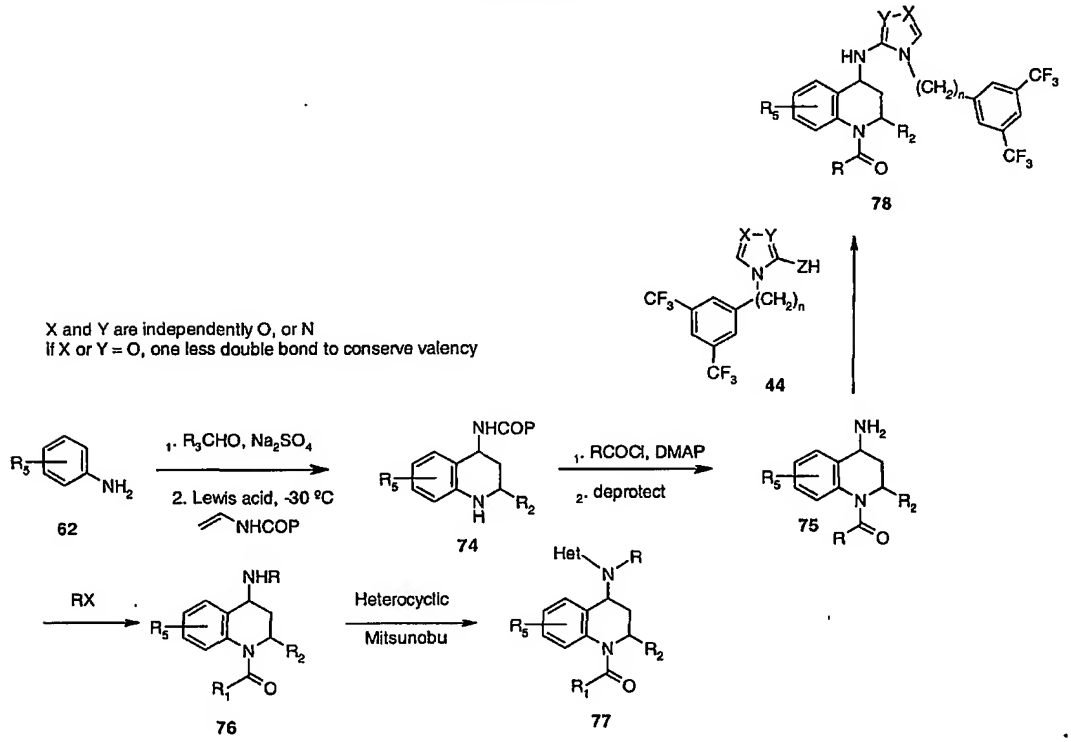
Scheme 10



Compounds of the Formula I may also be prepared as shown in Schemes 10 and 11, in which the intermediate tetrahydroquinoline-4-ones **64** are transformed into benzylic amine adducts. This may be achieved by a number of methods, including reductive amination with a primary amine surrogate (such as hydroxylamine, hydrazine, ammonium chloride, benzophenoneimine, among others), to provide a primary amine, as shown in Scheme 10, or may be incorporated into the ring construction sequence, as shown in Scheme 11, below, by chemistry known to one of ordinary skill in the art (Hadden, M.; Nieuwenhuyzen, M.; Potts, D.; Stevenson, P. J.; Thompson, N. *Tetrahedron* **2001**, *57*, 5615; Crousse, B.; Begue, J.-P.; Bonnet-Delpon, D. *J Org Chem* **2000**, *65*, 5009). Schiff base formation by treatment of the amine with a benzaldehyde is followed by treatment with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran or methanol, to achieve the benzylic amine adducts **69** (or alternatively, displacement of an activated benzylic substrate, such as a mesylate, tosylate or bromide) provides the benzylamine product. This is followed by treatment with an activated heteroaryl (heterocyclic aryl) substrate, such as a mesylate, tosylate or bromide in the presence of a base to produce dibenzylic products, as shown in Scheme 9. In a reverse fashion, formation of a Schiff base of tetrahydroquinoline-4-amines with a heteroaromatic

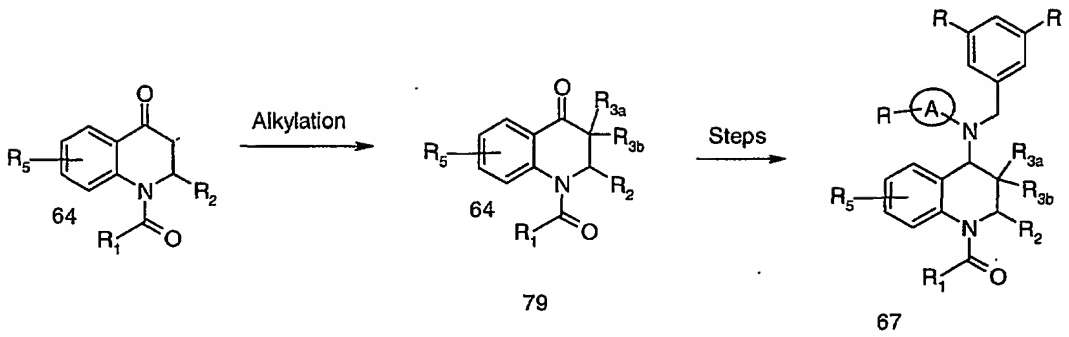
aldehyde, followed by treatment with a reducing agent such as sodium borohydride in an appropriate solvent, such as tetrahydrofuran or methanol (or alternatively, displacement of an appropriately activated heteroaryl substrate, such as a mesylate, tosylate or bromide) achieves the benzylic heteroaromatic amine adduct. This is followed by treatment with an activated benzylic substrate, such as a mesylate, tosylate or bromide in the presence of a base to produce dibenzylic products, as shown in Scheme 10.

Scheme 11



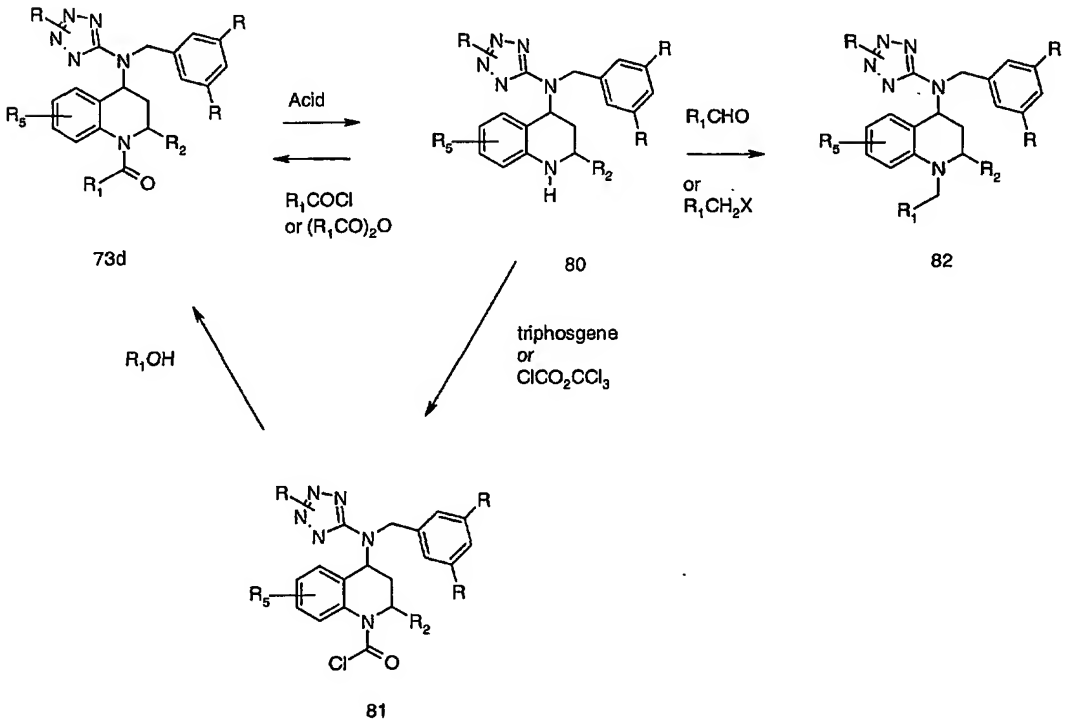
Compounds of Formula I may be similarly prepared following the procedure of Scheme 11

Scheme 12



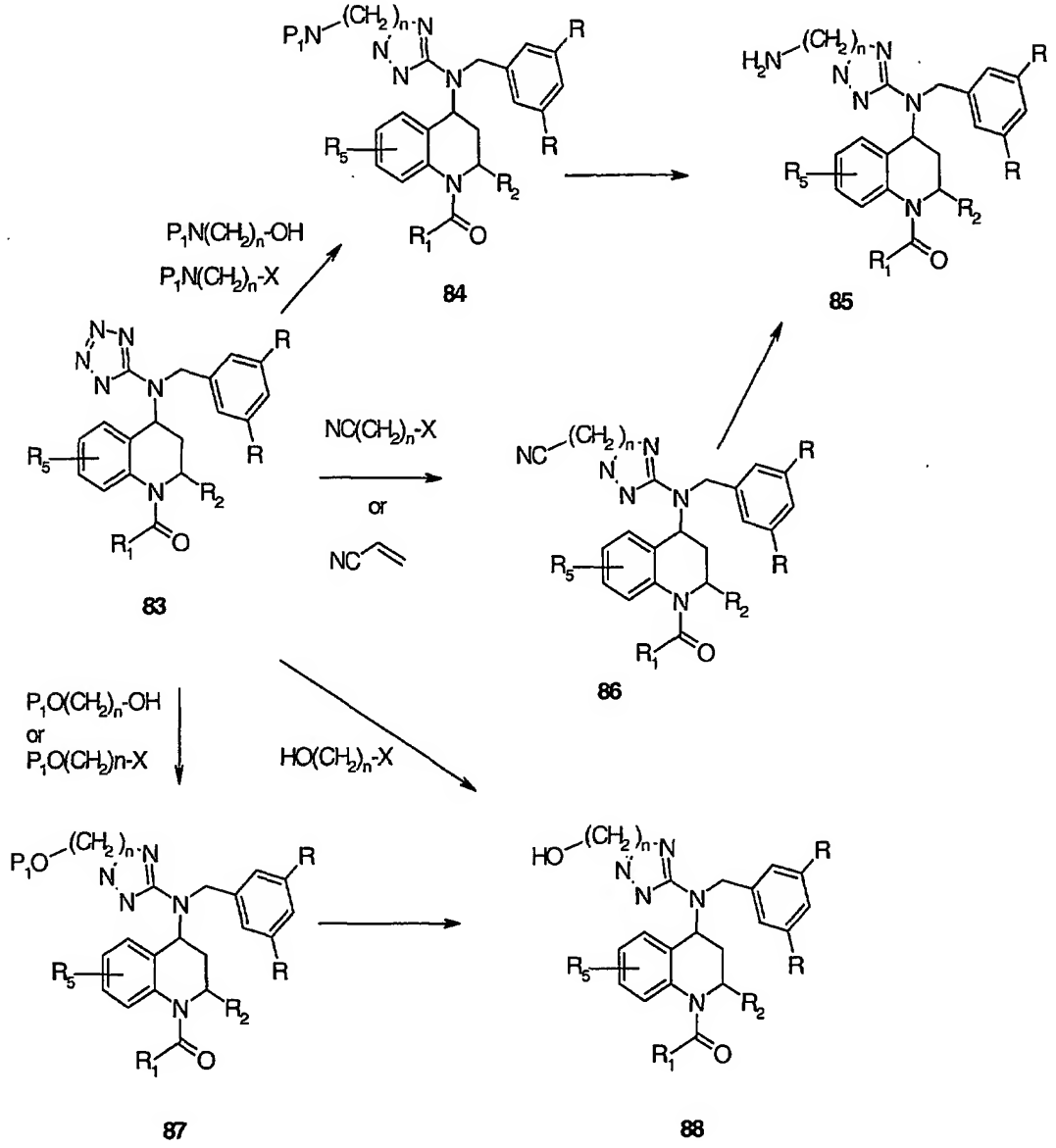
In Scheme 12, compound **64** can be treated with a base such as sodium hydride or lithium diisopropylamide or lithium bis(trimethylsilyl)amide in a solvent such as DMF or tetrahydrofuran. Alkylation with the appropriately substituted halide or mesylate or tosylate may form compound **79** where R3a and R3b can be the same or different. Conversion of **79** to **67** is as described, for example above in Scheme 10.

Scheme 13



As shown in Scheme 13, compound **73d** may be hydrolyzed to the corresponding amine **80**, and may be further acylated using standard procedures by one skilled in the art to provide **73d**. Or alteratively, **80** can be treated with triphosgene or trichloromethyl-choroformate to provide **81**. Compound **81** can afford compound **73d** by reaction with the appropriate alcohols. Also, compound **80** can be alkylated by methods known in the art such as treating **80** with base and an alkyl halide, tosylate or the like, to afford **82**. In still other alternatives, compound **82** can be obtained using reductive amination conditions.

Scheme 14



As shown in Scheme 14, tetrazole **83** can be alkylated with the appropriate protected aminoalcohol under Mitsunobu conditions or with the appropriate protected aminoalkylbromide, iodide or mesylate, (e.g. where P1 is the protecting group) or the like in the presence of base to provide a protected aminoalkyltetrazole **84**. Removal of P1 using methods well known in the art can yield compound **85**. Alternatively, tetrazole **83** can be alkylated with the appropriate alkylcyano bromide or with the appropriate acrylonitrile under Michael reaction conditions. Cyano derivative **86** can be then reduced

to the corresponding amine **85**. Tetrazole **83** can be alkylated using the appropriate alcohol under Mitsunobu conditions, or with the appropriate alkyl halide or the like in the presence of base to provide **87**. Removal of P1 using methods well known in the art can yield compound **88**. Alternatively hydroxyalkyltetrazole **88** can be obtained by alkylation of **83** with the corresponding halide in the presence of base.

Assays

The following assay protocol and result(s) thereof demonstrating the utility and efficacy of the compounds and/or methods of the current invention are given for the purpose of illustration and are not meant to be limiting in any way.

In Vitro CETP Inhibitor Assay: SPA Assay

An in vitro Scintillation proximity assay (SPA) has been used to evaluate the ability of compounds of this invention to inhibit the transfer of radiolabeled cholesterol esters between HDL and LDL. This assay monitors the inhibition of the transfer of [^{3}H]cholesterol esters from HDL (Amersham) to biotinylated LDL (Amersham) by a CETP source. The CETP source for this assay can be produced by AV-12 cells that have been created to express human CETP. The radiolabeled cholesterol ester is transferred in a HEPES-NaCl based buffer, after thirty minutes incubation the reaction is stopped and the biotinylated LDL is bound to streptavidin/scintillant coated SPA beads (Amersham). The radioactive signal is measured in a Packard 96-well scintillation TopCounter with window settings fully open. A decrease in radioactive signal from the LDL relative to a standard indicates the ability of compounds to inhibit the activity of CETP. Preferred compounds of the invention evaluated according to this assay protocol exhibit CETP inhibition at concentrations of less than 100 micromolar.

Alternatively, other CETP sources can be used to mediate the transfer of radiolabeled cholesterol ester in this assay. For example, endogenous CETP from human plasma, CETP from mice that express human CETP, and endogenous CETP from hamsters can be used as the CETP source in this assay.

Buffers other than HEPES-NaCl based buffer can be used in this assay, for example, human plasma, mouse plasma or a Tris-bufer that is high in albumin may be used.

It will be understood by those skilled in the art that other sources of radioactivity may be used to track the CETP activity in this assay.

Additionally, radio labeled-LDL may be used in this assay.

In Vivo Assay of CETP Activity

Syrian Golden Hamsters, which express endogenous CETP, can be used to assess the activity of the compounds *in vivo*. Test compounds are administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood/plasma can be obtained. The CETP activity can be determined by a method similar to that described above for the *in vitro* CETP activity assay, with the modification that plasma from the treated animals is used as the CETP source in the assay.

A strain of transgenic mice that express human CETP (Taconic, Germantown, NY) can also be used to test compounds of this invention. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood/plasma can be obtained. The CETP activity can be determined by a method similar to that described above for the *in vitro* CETP activity assay, with the modification that plasma from the treated animals is used as the CETP source in the assay.

Alternatively, a strain of transgenic mice that express both human CETP and human apolipoprotein A-1 (Taconic, Germantown, NY) can be used to test compounds of this invention. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to one week. At various times after dosing, ranging from 4h to 48h, blood/plasma is obtained. CETP activity can be determined by a method similar to that described for the *in vitro* CETP activity assay, with the modification that plasma from the treated animals is used as the CETP source in the assay.

In Vivo Assay of Plasma Lipids

Activity of compounds of this invention in vivo can be evaluated by comparing the level of elevation of HDL cholesterol relative to a control by a given amount of a compound in a CETP-containing animal species. A strain of transgenic mice that express both human CETP and human apolipoprotein A-1 (Taconic, Germantown, NY) can be

used to evaluate compounds of this invention. Test compounds are administered to the animals once orally in selected aqueous or oil based vehicles. At various times after dosing, ranging from 4h to 24h, blood is obtained. The blood is allowed to clot, and serum is obtained from the clotted blood by centrifugation. The HDL cholesterol levels in the serum can be determined by known procedures using HDL-C plus reagents (Roche/Hitachi, Indianapolis, IN) with a clinical chemistry analyzer (Roche/Hitachi, Indianapolis, IN). Additional serum lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL, and HDL fractions are analyzed by enzymatic methods after precipitation or size exclusion chromatography. An example of the elevation of HDL cholesterol levels at 8hr is summarized in Table 1.

Table 1

Elevation of HDL cholesterol levels at 8 hr

Compound of Example No.	Single Oral Dose (mg/kg)	% HDL cholesterol increase
1	30	125
4	30	194
5	30	134
8	30	120
10	30	139
12	30	153
13	30	185
19	30	226

The efficacy of compounds of the invention in vivo can also be evaluated utilizing Syrian Golden Hamsters. The compounds can be tested in hamsters made hypercholesterolemic by feeding a high fat high cholesterol diet for a minimum of two weeks or in non-hypercholesterolemic hamsters fed normal chow for two weeks. Test compounds can be administered orally in selected aqueous or oil based vehicles for up to 1 week. Serum from the animals can be obtained, and lipids can be analyzed by enzymatic methods. Lipids in the VLDL, LDL, and HDL fractions can be analyzed by known enzymatic methods after precipitation or size exclusion chromatography.

Alternatively, a strain of transgenic mice that expresses human CETP (Taconic, Germantown, NY) can be used to test the efficacy of the compounds of this invention.

The hCETP mice can be made hypercholesterolemic by feeding a high fat chow diet such as TD 88051, as described by Nishina et al. (J Lipid Res., 31, 859-869 (1990)) for at least two weeks before the start of the study. Test compounds can be administered orally to the animals in selected aqueous or oil based vehicles for up to 1 week. Serum can be obtained from the animals. Lipids from the serum can be analyzed by enzymatic methods. Lipids in the VLDL, LDL and HDL fractions are analyzed by enzymatic methods after precipitation or size exclusion chromatography.

Method of Treatment

As used herein, the term "effective amount" means an amount of compound of the present invention, i.e., Formula I, which is capable of alleviating the symptoms of the various pathological conditions herein described. A specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, but not limited to: the compound administered, the route of administration, the state of being of the patient, and the pathological condition being treated. A typical daily dose will contain a nontoxic dosage level of from about 0.01 mg to about 1000 mg/day of a compound of the present invention. Preferred daily doses generally will be from about 1 mg to about 250 mg/day.

The compounds of this invention may be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. These compounds preferably are formulated prior to administration, the selection of which will be decided by the attending physician. Thus, another aspect of the present invention is a pharmaceutical composition comprising an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, solvate, prodrug, enantiomer or prodrug thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The total active ingredients in such formulations comprises from 0.1% to 99.9% by weight of the formulation.

The term "pharmaceutically acceptable" as used herein means that the carrier, diluent, excipients and salt are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Pharmaceutical formulations of the present invention may be prepared by procedures known in the art using well-known and readily available ingredients. For

example, the compounds of Formula I can be formulated with common excipients, diluents, or carriers, and formed into tablets, capsules, suspensions, powders, and the like. Non limiting examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, sugars, mannitol, and silicic derivatives; binding agents such as carboxymethyl cellulose and other cellulose derivatives, alginates, gelatin, and polyvinyl-pyrrolidone; moisturizing agents such as glycerol; disintegrating agents such as calcium carbonate and sodium bicarbonate; agents for retarding dissolution such as paraffin; resorption accelerators such as quaternary ammonium compounds; surface active agents such as cetyl alcohol, glycerol monostearate; adsorptive carriers such as kaolin and bentonite; and lubricants such as talc, calcium, and magnesium stearate, and solid polyethyl glycols.

The compounds also may be formulated as elixirs or solutions for convenient oral administration or as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. Additionally, the compounds are well suited to formulation as sustained release dosage forms and the like. The formulations can be so constituted that they release the active ingredient only or preferably in a particular physiological location, possibly over a period of time. The coatings, envelopes, and protective matrices may be made, for example, from polymeric substances or waxes.

Compounds of Formula I, generally, will be administered in a convenient formulation as determined by the attending physician. The following formulation examples are only illustrative and are not intended to limit the scope of the present invention.

Formulations

Compounds of the invention may be formulated following one or more of the formulation examples, procedures, protocols or mixing ratios below. In the formulations which follow, the term "Active Ingredient" as used herein means a compound of Formula I, a salt, solvate, racemate, enantiomer diastereomer, mixture of diastereomers, prodrug thereof, or a combination of a compound of Formula I and other effective agents for the treatment or prevention of dyslipidemia, atherosclerosis, or other co-morbid conditions and symptoms.

Formulation 1: Gelatin Capsules

Hard gelatin capsules can be prepared according to the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.1 - 1000
Starch, NF	0 - 650
Starch flowable powder	0 - 650
Silicone fluid 350 centistokes	0 - 15

The formulation above may be changed in compliance with the reasonable variations provided.

Formulation 2: Tablets

A tablet formulation each tablet containing 2.5 – 1,000 mgs of active ingredient can be prepared according to the following:

Ingredient	Quantity (mg/tablet)
Active ingredient	2.5 - 1000
Cellulose, microcrystalline	200 - 650
Silicon dioxide, fumed	10 - 650
Stearate acid	5 - 15

The components are blended and compressed to form tablets.

Formulation 3: Tablets

Alternatively, tablets each containing 25 - 1000 mg of active ingredient can be prepared according to the following:

Ingredient	Quantity (mg/tablet)
Active ingredient	25 - 1000
Starch	45

Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and thoroughly blended. The solution of polyvinylpyrrolidone is mixed with the blended powders. The resulting mixture is then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 U.S. sieve, are then added to the granules, which after mixing, are compressed on a tablet machine to yield tablets.

Formulation 4: Suspensions

A suspensions containing 0.1 - 1000 mg of medicament per 5 ml dose can be prepared as follows:

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.1 - 1000 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified water to	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and then blended with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor, and color are diluted with an amount of purified water and

added, with stirring, to the paste. Sufficient purified water is then added to provide the suspension at the desired volume (or concentration).

Formulation 5: Aerosol

An aerosol solution can be prepared as follows:

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30 °C, and transferred to a filling device. The desired amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Formulation 6: Intravenous Solution

A solution suitable for intravenous administration can be prepared as follows:

Ingredient	Quantity
Active ingredient	50 mg
Isotonic saline	1,000 mL

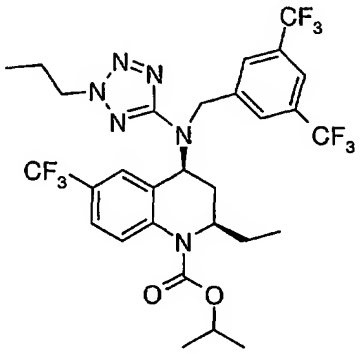
A solution comparing the above ingredients can be intravenously administered to a patient at a rate of about 1 mL per minute or as prescribed by a physician.

Examples

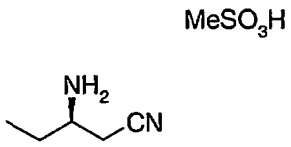
Compounds of the invention may be prepared following or in analogy to one or more of the Examples and procedures described below.

Example 1

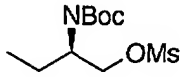
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Step 1. Preparation of (R)-3-Aminopentanenitrile methanesulfonic acid salt.

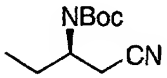


Step 1.1. Preparation of methanesulfonic acid 2-tert-butoxycarbonylamino-butyl ester.



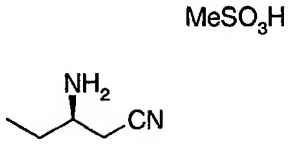
Add dropwise BOC anhydride (240 g 1.10 mol) in ethyl acetate (180 mL) to a solution of R-(-)-2-amino-1-butanol (94 g, 1.00 mol) in ethyl acetate (490 mL). Stir the mixture for 30 min. Add tetramethylenenediamine (168 mL, 1.11 mol) and cool down to 10 °C. Add slowly methanesulfonyl chloride (86 mL, 1.11 mmol) and stir for 2 h at 10 °C, then filter and wash the solids with ethyl acetate (90 mL). Add hexane to the filtrate, cool to 5 °C and stir for 2 h. Filter and wash with hexane (2.6 L) to afford the title compound (251 g, 94%).

Step 1.2. Preparation of (2-cyano-1-ethyl-ethyl)-carbamic acid tert-butyl ester.



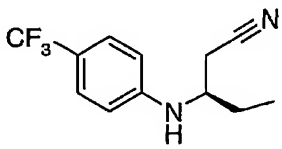
Mix sodium cyanide (36.9 g, 0.73 mol) and dimethylformamide (741 mL) and stir the mixture at 35 °C for 30 minutes. Add tetrabutyl ammonium bromide (18.3 g, 56.2 mmol) and stir at 35 °C for 2 h. Add methanesulfonic acid 2-tert-butoxycarbonylamino-butyl ester (150 g, 0.56 mol) and stir at 35 °C overnight. Pour the mixture onto water (3.2 mL) and t-butyl methyl ether (1.5 L). Separate the layers. Extract the aqueous phase with t-butyl methyl ether. Wash the organic layers with water and brine, dry over anhydrous NaSO4 and remove the solvent under reduced pressure. Treat the residue with hexane (40 mL) and heat to reflux until the solid is complete dissolved. Cool down to room temperature. Collect the solid by filtration washing with hexane and dry it under vacuum to afford the title compound (85.2 g, 77%).

Step 1.3. Preparation of (R)-3-aminopentanenitrile methanesulfonic acid salt.



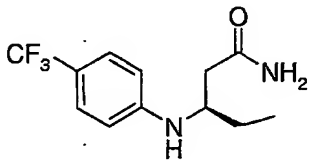
Add methane sulphonic acid (31.8 mL, 491 mmol) to a solution of (2-cyano-1-ethyl-ethyl)-carbamic acid tert-butyl ester (54.1 g, 0.27 mol) in dry tetrahydrofuran (350 mL). Heat the mixture to 40 °C for 30 minutes, to 45 °C for 1 h and to 65 °C for 5 h, then cool down to room temperature. Collect the solid by filtration to afford the title compound (43.4 g, 82%).

Step 2. Preparation of (3R)-3-(4-trifluoromethyl-phenylamino)-pentanenitrile.



Add sodium carbonate (9.33 g, 88 mmol) to a solution of (R)-3-aminopentanenitrile methanesulfonic acid salt (10 g, 51.5 mmol) in dichloromethane (70 mL). Stir the mixture at room temperature under nitrogen for 2 h. Filter the solid and wash with dichloromethane. Remove the solvent under reduced pressure. To the residue add toluene (67 mL), chloro-4-(trifluoromethyl)benzene (10.4 mL, 77.3 mmol) and cesium carbonate (25.2 g, 77.3 mmol) and purge the mixture with nitrogen. In another flask treat a mixture of 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (223 mg, 0.57 mmol), phenylboronic acid (98 mg, 0.80 mmol) and tetrahydrofuran (4.2 mL) with palladium acetate (167 mg, 0.74 mmol). Purge the mixture with nitrogen and stir at room temperature for 15 minutes. Add the catalyst solution to the flask containing chloro-4-(trifluoromethyl)benzene via cannula. Heat the mixture under nitrogen at 80 °C for 16 h, cool down to room temperature and filter through Celite®. Wash the solids with toluene and concentrate under reduced pressure to afford the title compound (12.27 g, 98%). 1H NMR (CDCl3, 300 MHz) δ 1.06 (t, J = 7.3 Hz, 3H), 1.66-1.92 (m, 2H), 2.59 (dd, J1 = 4.1, J2 = 16.5 Hz, 1H), 2.70 (dd, J1 = 5.6, J2 = 16.5 Hz, 1H), 3.68 (m, 1H), 4.49 (m, 1H), 6.61 (d, J = 8.9 Hz , 2H), 7.43 (d, J = 8.9 Hz , 2H). MS (ES+): 243 (M+H).

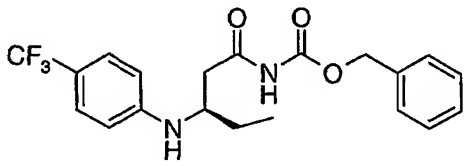
Step 3. Preparation of (3R)-3-(4-trifluoromethyl-phenylamino)-pentanoic acid amide.



Add concentrated sulfuric acid (24 mL) to water (3 mL), cool the mixture below 35 °C and add it to a solution of (3R)-3-(4-trifluoromethyl-phenylamino)-pentanenitrile (10 g, 41.3 mmol) in toluene (60 mL). Heat the mixture to 35 °C for 15 h. Separate the aqueous layer and treat it (ice cooling) with water (277 mL), NaOH (31 g) and diethyl ether (116 mL). Separate the layers, extract the aqueous phase with diethyl ether, then wash the organic layers with saturated sodium hydrogen carbonate, dry over anhydrous Na2SO4 and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with dichloromethane/methanol (97:3), to afford the title

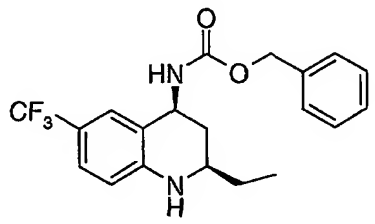
compound (8.91 g, 83%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.98 (t, J = 7.3 Hz, 3H), 1.50-1.80 (m, 2H), 2.45 (d, J = 5.7 Hz, 2H), 3.77 (m, 1H), 5.61 (m, 2H), 6.65 (d, J = 8.9 Hz , 2H), 7.39 (d, J = 8.9 Hz , 2H). MS (ES+): 261 (M+H).

Step 4. Preparation of (3R)-[3-4-trifluoromethyl-phenylamino)-pentanoyl]-cabamic acid benzyl ester.



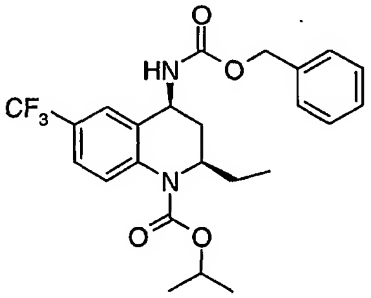
Add benzyl chloroformate (5.76 mL, 40.4 mmol) under nitrogen to a solution of (3R)-3-(4-trifluoromethyl-phenylamino)-pentanoic acid amide (8.73 g, 33.6 mmol) in diethyl ether (43 mL) cooled to –10 °C, then add a solution 1.0 M of lithium t-butoxide in tetrahydrofuran (80.5 mL , 80.5 mmol) maintaining the temperature below 0 °C. 15 minutes after the addition is complete, quench by adding the mixture to diethyl ether (43 mL) and 1.5 M hydrochloric acid (56 mL). Separate the layers. Wash the organic phase with brine, dry over anhydrous Na2SO4 and remove the solvent under reduced pressure. Purify the residue by chromatography, eluting with hexanes/ethyl acetate (3:1), to afford the title compound (12.7 g, 96%). ^{1}H NMR (acetone-D_6, 300 MHz) δ 0.96 (t, J = 7.3 Hz, 3H), 1.50-1.80 (m, 3H), 2.80-3.05 (m, 2H), 3.96 (m, 1H), 5.16 (s, 2H), 5.49 (m, 1H), 6.75 (d, J = 8.9 Hz, 2H), 7.25-7.50 (m, 7H). MS (ES+): 395 (M+H).

Step 5. Preparation of (2R,4S)-(2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester.



Add sodium borohydride (833 mg, 22.1 mmol) to a solution of (3R)-[3-4-trifluoromethyl-phenylamino)-pentanoyl]-carbamic acid benzyl ester (12.5 g, 31.8 mmol) in ethanol (87 mL) cooled to –10 °C. Then add slowly a solution of MgCl2.6H2O (6.78 g, 33.3 mmol) in water (14 mL). After complete addition, raise the temperature to 0 °C and stir the mixture for 30 min. Quench the reaction by adding dichloromethane (125 mL), 1 M hydrochloric acid (125 mL) and citric acid (15.3 g, 79.6 mmol). Stir the mixture for 3 h at room temperature. Separate the layers. Add water (63 mL) and citric acid (9.18 g, 47.8 mmol) to the organic phase and stir for 20 min. Separate the layers. Extract the aqueous phase with dichloromethane. Wash the organic layers with brine, dry over anhydrous Na2SO4 and remove the solvent under reduced pressure to afford the title compound (11.8 g, 98%). ^{1}H NMR (acetone-D_6, 300 MHz) δ 1.00 (t, J = 7.3 Hz, 3H), 1.50-1.80 (m, 3H), 2.20 (m, 1H), 3.49 (m, 1H), 4.96 (m, 1H), 5.14 (d, J = 12.5 Hz, 1H), 5.20 (d, J = 12.5 Hz, 1H), 5.66 (bs, 1H), 6.65 (d, J = 8.5 Hz, 1H), 6.71 (m, 1H), 7.19 (m, 1H) 7.30-7.50 (m, 5H). MS (ES+): 379 (M+H).

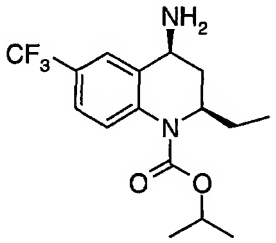
Step 6. Preparation of (2R,4S)-4-Benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add a solution 1.0 M of isopropyl chloroformate in toluene (109 mL, 109 mmol) to a solution of (2R,4S)-(2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (11.8 g, 31.1 mmol) and pyridine (7.6 mL, 93.3 mmol) in dichloromethane (200 mL) at 0 °C under nitrogen. Allow the mixture to reach room temperature and stir for 14 h. Cool to 0 °C and add 1 M potassium hydroxide. Separate the layers. Wash the organic phase with 1 M hydrochloric acid and brine, dry over anhydrous sodium sulfate and remove the solvent under reduced pressure to afford the

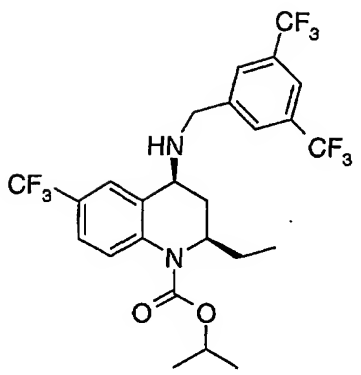
title compound (14.4 g, quantitative). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 7.3 Hz, 3H), 1.26 (d, J = 6.1 Hz, 3H), 1.31 (d, J = 6.1 Hz, 3H), 1.35-1.70 (m, 3H), 2.55 (m, 1H), 4.47 (m, 1H), 4.70-4.98 (m, 2H), 5.03 (septuplet, J = 6.1 Hz, 1H), 5.20 (s, 2H), 7.30-7.62 (m, 8H). (MS (ES+): 465 (M+H).

Step 7. Preparation of (2R,4S)-4-Amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



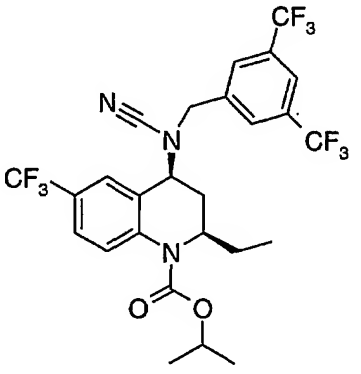
Stir a mixture of (2R,4S)-4-benzyloxycarbonylamino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (14.4 g, 30.9 mmol) and 10% Pd/C (3.08 g) in ethyl acetate (303 mL) at room temperature under an atmosphore of hydrogen for 1 h. Then filter over Celite® and wash the solids with dichloromethane. Remove the solvent under reduced pressure to afford the title compound (10.3 g, quantitative). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 7.3 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.31 (d, J = 6.1 Hz , 3H), 1.30-1.75 (m, 3H), 2.50 (m, 1H), 3.83 (dd, J1 = 4.4, J2 = 11.3 Hz, 1H), 4.40 (m , 1H), 5.02 (septuplet, J = 6.1 Hz , 1H), 7.45-7.55 (m, 2H), 7.71 (bs, 1H).

Step 8. Preparation of (2R,4S)-4-(3,5-Bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



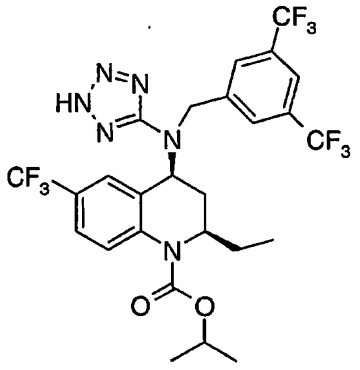
Add 3,5-bis-trifluoromethyl benzaldehyde (2 mL, 12.1 mmol), acetic acid (0.69 mL, 12.1 mmol) and sodium triacetoxyborohydride (3.85 g, 18.2 mmol) to a solution of (2R,4S)-4-amino-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (4.0 g, 12.1 mmol) in 1,2-dichloroethane (43 mL) and stir at room temperature overnight. Then add saturated aqueous sodium bicarbonate and dichloromethane, separate the layers and dry the organic phase over anhydrous Na2SO4, filter and remove the solvents under vacuum. Chromatograph the residue over silica gel, eluting with hexanes/ethyl acetate (4:1) to afford the title compound, 5.11 g (76%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 7.3 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.31 (d, J = 6.1 Hz, 3H), 1.30-1.75 (m, 3H), 2.67 (m, 1H), 3.60 (m, 1H), 4.10 (d, J = 14.5 Hz , 1H), 4.19 (d, J = 14.5 Hz , 1H), 4.40 (m, 1H), 5.10 (septuplet, J = 6.1 Hz , 1H), 7.48-7.56(m, 2H), 7.78 (s, 1H), 7.81 (s, 1H), 7.94 (bs, 1H). (MS (ES+): 557 (M+H).

Step 9. Preparation of (2R,4S)-4-[(3,5-Bis-trifluoromethyl-benzyl)-cyano-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



To a suspension of 60% sodium hydride in mineral oil (267 mg, 6.68 mmol) in dimethyl sulfoxide (31 mL) under nitrogen atmosphere, add (2R,4S)-4-(3,5-bis-trifluoromethyl-benzylamino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (3.10 g, 5.57 mmol) followed by dimethylformamide (6.2 mL). Then add cyanogen bromide (1.81 g, 16.7 mmol) and stir the mixture at room temperature for 1.5 h. Then add more 60% sodium hydride in mineral oil (150 mg, 3.75 mmol) and cyanogen bromide (1.02 g, 9.39 mmol) and stir for 1.5 h. Add water and ethyl acetate. Extract with ethyl acetate. Wash the organic layers with water and brine. Dry the organic phase over anhydrous Na2SO4, filter and remove the solvents under vacuum. Purify the residue by flash chromatography, eluting with hexanes/ethyl acetate (4:1) to afford the title compound (2.3 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 7.3 Hz, 3H), 1.24 (d, J = 6.1 Hz, 3H), 1.31 (d, J = 6.1 Hz , 3H), 1.40-1.87 (m, 3H), 2.64 (m, 1H), 3.88 (dd, J1 = 4.6, J2 = 11.7 Hz, 1H), 4.42 (m, 1H), 4.49 (d, J = 15.1 Hz , 1H), 4.66 (d, J = 15.1 Hz , 1H), 5.01 (septuplet, J = 6.1 Hz , 1H), 7.53(bs, 1H), 7.78 (s, 1H), 7.59 (bs, 2H), 7.88 (bs, 2H), 7.94 (bs, 1H). MS (ES+): 582 (M+H).

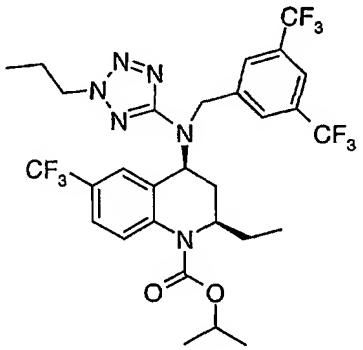
Step 10. Preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add azidotributyltin (3.01 mL, 11 mmol) to a solution of (2R,4S)-4-[(3,5-bis-trifluoromethyl-benzyl)-cyano-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (3.20 g, 5.50 mmol) in toluene (58 mL). Stir the mixture for 2 h at 80 °C under nitrogen. Cool down the mixture to room temperature, add ethyl acetate (76 mL) and 1 M hydrochloric acid (140 mL) and stir at room

temperature for 1 h. Separate the layers, wash the organic phase with saturated potassium fluoride, then with brine, dry over anhydrous sodium sulfate, filter and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with dichloromethane/methanol (95/5), to provide 3.19 g (quantitative) of the title compound. ^{1}H NMR (MeOD, 300 MHz) δ 0.80 (t, J = 7.3 Hz, 3H), 1.27 (d, J = 6.5 Hz, 3H), 1.33 (d, J = 6.1 Hz, 3H), 1.40-1.90 (m, 3H), 2.43 (m, 1H), 4.43 (m, 1H), 4.70-5.30 (m, 4H), 7.12 (bs, 1H), 7.52 (m, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.83 (bs, 1H), 7.98 (bs, 2H). MS (ES-): 623 (M-H).

Step 11. Preparation of (2R,4S)-4-[(3,5-Bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

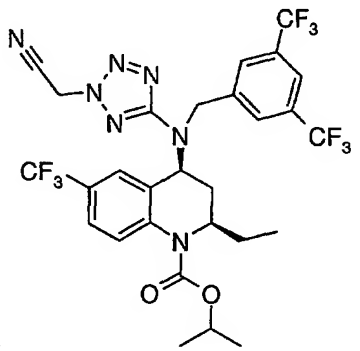


Add in one portion triphenyl phosphine (109 mg, 0.42 mmol) followed by addition of a solution of diethyl azodicarboxylate in toluene (40%, 0.13 mL, 0.42 mmol) to a solution of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (130 mg, 0.21 mmol) and 1-propanol (0.16 mL, 2.1 mmol) in dichloromethane (5 mL). Stir the reaction mixture at room temperature under nitrogen overnight. Then add more 1-propanol (0.16 mL, 2.1 mmol), triphenyl phosphine (109 mg, 0.42 mmol) and diethyl azodicarboxylate in toluene (40%, 0.13 mL, 0.42 mmol) and stir for 6 h. Remove the solvents under reduced pressure. Purify the residue by flash chromatography, eluting with hexane/ethyl acetate (4:1) to afford the title compound (75 mg, 54 %). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H), 1.28 (d, J = 6.3 Hz , 3H), 1.33 (d, J = 6.1 Hz , 3H), 1.40-1.80 (m, 3H), 1.95 (m, 2H), 2.40 (m, 1H), 4.35-4.50

(m, 3H), 4.98-5.10 (m, 2H), 7.07 (bs, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.80 (bs, 3H). MS (ES+): 667 (M+H).

Example 2

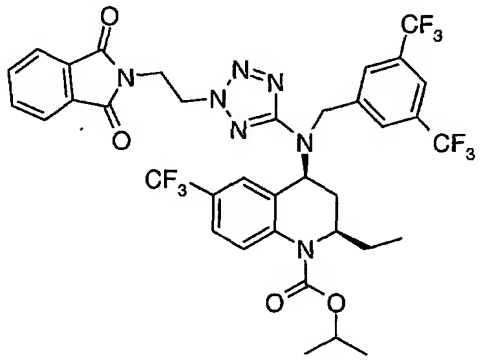
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyanomethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add potassium carbonate (68 mg, 0.64 mmol) and bromoacetonitrile (0.044 mL, 0.64 mmol) to a solution of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1, step 10**) (200 mg, 0.32 mmol) in dimethylformamide (1 mL) and acetone (1 mL) at room temperature. Stir the mixture at room temperature overnight. Add water and dichloromethane. Separate the layers, wash the organic phase with brine, dry over anhydrous Na2SO4, filter and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with hexane/ethyl acetate (3:1), to provide 90 mg (42 %) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 7.5 Hz, 3H), 1.28 (d, J = 6.3 Hz , 3H), 1.33 (d, J = 6.1 Hz , 3H), 1.40-1.80 (m, 3H), 2.40 (m, 1H), 4.41 (m, 1H), 4.95-5.20 (m, 2H), 5.34 (d, J = 17.4 Hz , 1H), 5.40 (d, J = 17.4 Hz , 1H) 7.03 (bs, 1H), 7.52 (m, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.79 (bs, 2H), 7.82 (bs, 1H). MS (ES+): 664 (M+H).

Example 3

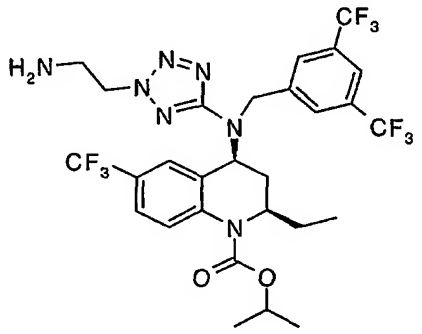
Synthesis of (2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing 1-propanol with N-(2-hydroxyethyl)-phtalimide in **Example 1, step 11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.77 (t, J = 7.5 Hz, 3H), 1.27 (d, J = 6.3 Hz , 3H), 1.32 (d, J = 6.1 Hz , 3H), 1.40-1.80 (m, 3H), 2.37 (m, 1H), 4.07-4.23 (m, 2H), 4.28-4.44 (m, 2H), 4.65-4.47 (m, 2H), 4.95-5.12 (m, 2H), 7.20 (bs, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.66-7.84 (m, 7H). MS (ES+): 798 (M+H).

Example 4

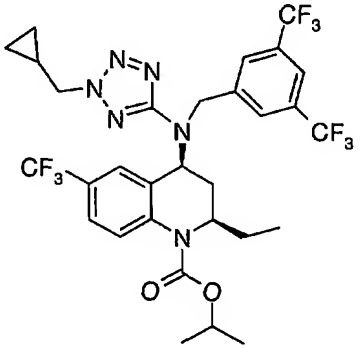
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add hydrazine hydrate (0.16 mL, 3.3 mmol) to a solution of (2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 3**) (174 mg, 0.22 mmol) in methanol (12 mL). Heat the mixture at reflux for 2 h under nitrogen. Cool down to room temperature, then remove the solvent under reduced pressure. Purify the residue by chromatography, eluting with dichloromethane/methanol with ammonia 2 M (20:1) to afford the title compound (111 mg, 76%). ^{1}H NMR (MeOD, 300 MHz) δ 0.82 (t, J = 7.5 Hz, 3H), 1.26 (d, J = 6.1 Hz , 3H), 1.32 (d, J = 6.1 Hz , 3H), 1.40-1.80 (m, 3H), 2.47 (m, 1H), 3.10 (m, 2H), 4.35-4.60 (m, 3H), 4.94-5.20 (m, 2H), 7.05 (bs, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.86 (bs, 1H), 8.04 (bs, 2H). MS (ES+): 668 (M+H).

Example 5

Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

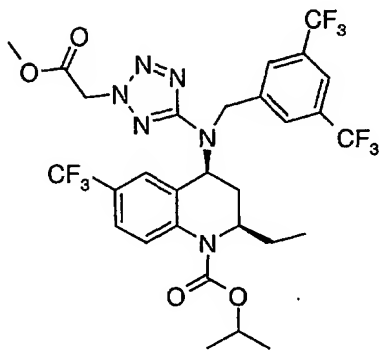


Add potassium carbonate (56 mg, 0.41 mmol) and (bromomethyl)cyclopropane (0.036 mL, 0.37 mmol) to a solution of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1, step 10**) (153 mg, 0.24 mmol) in dimethylformamide (0.5 mL) at room temperature. Stir the mixture at room temperature overnight. Add water and ethyl acetate. Separate the layers, dry the organic phase over anhydrous Na2SO4, filter and remove the solvent under reduced pressure. Purify the residue by flash

chromatography, eluting with hexane/ethyl acetate, to provide 74 mg (45%) of the title compound. MS (ES+): 679 (M+H).

Example 6

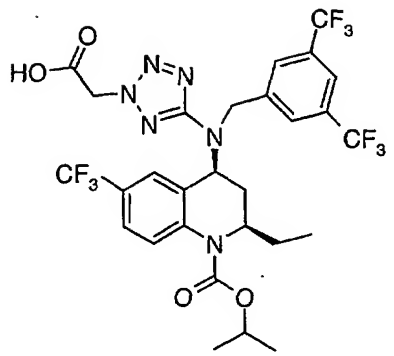
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-methoxycarbonylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add triethylamine (50 µl, 0.35 mmol) and methylbromoacetate (33 µl, 0.35 mmol) to a solution of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1, step 10**) (200 mg, 0.32 mmol) in acetonitrile (1 mL) at room temperature. Stir the mixture at room temperature overnight. Add 1 N hydrochloric acid and extract with dichloromethane. Separate the layers, dry the organic phase over anhydrous sodium sulfate, filter and remove the solvent under reduced pressure. Purify the residue by silica gel cartridge, eluting with hexane/ethyl acetate 20:1, to provide 180 mg (81%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.7 Hz, 3H), 1.28 (d, J = 6.5 Hz , 3H), 1.32 (d, J = 6.5 Hz , 3H), 1.41-1.79 (m, 4H), 2.35-2.43 (m, 1H), 3.77 (s, 3H), 4.35-4.44 (m, 1H), 4.60 (m, 1H), 4.97-5.12 (m, 2H), 5.24 (s, 2H), 7.06 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.80 (s, 3H). MS (ES+): 697 (M+H).

Example 7

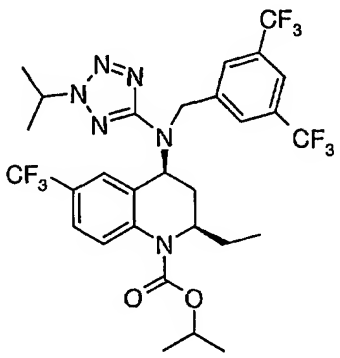
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-carboxymethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add 1 N NaOH solution (0.2 ml) to (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-methoxycarbonylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 6**) (45 mg, 0.065 mmol) in methanol (1 ml). Stir the mixture at room temperature overnight. Add 1 N hydrochloric acid and extract with ethyl acetate. Separate the layers, dry the organic phase over anhydrous sodium sulfate, filter and remove the solvent under reduced pressure to provide 31 mg (70%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.7 Hz, 3H), 1.27 (d, J = 6.1 Hz , 3H), 1.32 (d, J = 6.1 Hz , 3H), 1.41-1.55 (m, 2H), 1.65-1.76 (m, 2H), 2.34-2.43 (m, 1H), 4.34-4.44 (m, 1H), 4.62 (m, 1H), 4.97-5.12 (m, 2H), 5.27 (s, 2H), 7.06 (s, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.80 (s, 3H). MS (ES-): 681 (M-H).

Example 8

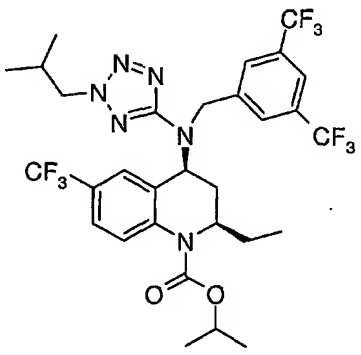
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-isopropyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing 1-propanol with 2-propanol in **Example 1, step 11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 7.5 Hz, 3H), 1.28 (d, J = 6.3 Hz , 3H), 1.33 (d, J = 6.1 Hz , 3H), 1.40-1.80 (m, 3H), 1.50-1.60 (m, 6H), 2.40 (m, 1H), 4.40 (m, 1H), 4.86 (septuplet, J = 6.7, 1H), 4.90-5.12 (m, 1H), 7.09 (bs, 1H), 7.49 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.78-7.86 (m, 3H). MS (ES+): 667 (M+H).

Example 9

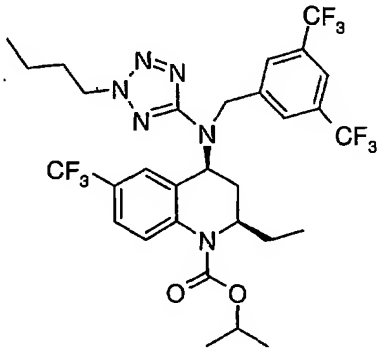
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-isobutyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing 1-propanol with isobutanol in **Example 1, step 11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 7.5 Hz, 3H), 0.89 (dd, J1 = 2.4 Hz, J2 = 6.9 Hz), 1.26 (d, J = 6.3 Hz , 3H), 1.32 (d, J = 6.1 Hz , 3H), 1.40-1.80 (m, 2H), 2.20-2.45 (m, 2H), 4.23 (d, J = 7.3 Hz, 1H), 4.40 (m, 1H), 4.97-5.14 (m, 2H), 7.05 (bs, 1H), 7.49 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.79 (bs, 3H). MS (ES+): 681 (M+H).

Example 10

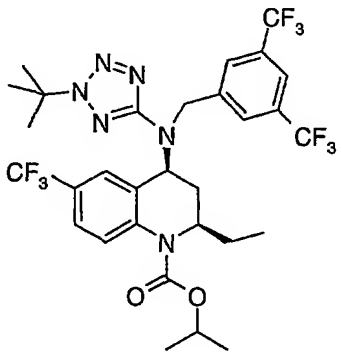
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-butyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing 1-propanol with 1-butanol in **Example 1, step 11**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.78 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.7 Hz), 1.20-1.90 (m, 7H), 1.27 (d, J = 6.1 Hz, 3H), 1.32 (d, J = 6.1 Hz, 3H), 2.39 (m, 1H), 4.30-4.50 (m, 3H), 4.95-5.15 (m, 2H), 7.06 (bs, 1H), 7.49 (m, 1H), 7.61 (d, J = 8.5 Hz, 1H), 7.80 (bs, 3H). MS (ES+): 681 (M+H).

Example 11

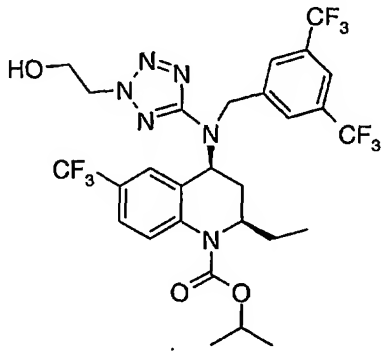
Synthesis of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-tert-butyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add tert-butanol (15 ul, 0.16 mmol) and concentrated sulfuric acid (4 mg, 0.04 mmol) to (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1, step 10**) (50 mg, 0.08 mmol) in trifluoroacetic acid (0.18 ml, 1.04 mmol). Stir the mixture at room temperature for 48 h. Purify the residue by silica gel cartridge, eluting with hexane/ethyl acetate 15:1, to provide 31 mg (56%) of the title compound. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.79 (t, J = 7.3 Hz, 3H), 1.27 (d, J = 6.1 Hz , 3H), 1.32 (d, J = 6.5 Hz , 3H), 1.46-1.77 (m, 4H), 1.65 (s, 9H), 2.36-2.44 (m, 1H), 4.36-4.46 (m, 1H), 4.66 (m, 1H), 4.99-5.10 (m, 2H), 7.09 (s, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.79-7.84 (m, 3H). MS (ES+): 681 (M+H).

Example 12

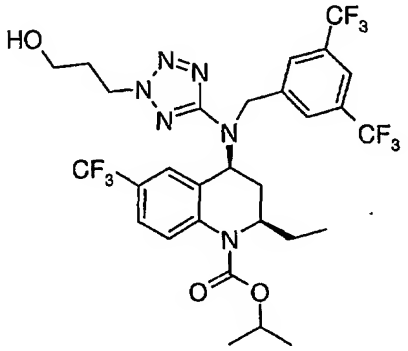
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-hydroxy-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 5**) by replacing (bromomethyl)cyclopropane with 2-bromoethanol. MS (ES+): 669 (M+H).

Example 13

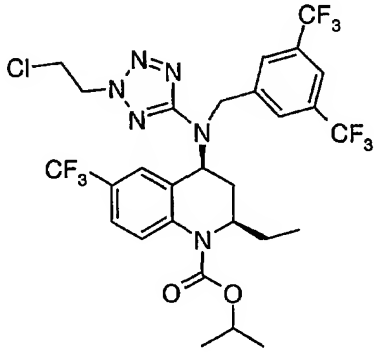
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 5**) by replacing (bromomethyl)cyclopropane with 3-bromo-1-propanol. MS (ES+): 683 (M+H).

Example 14

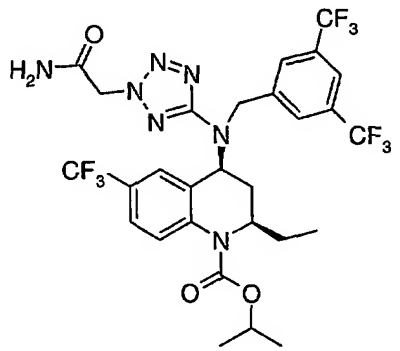
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-chloro-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 5**) by replacing (bromomethyl)cyclopropane with 1-bromo-2-chloroethane. MS (ES+): 688 (M+H).

Example 15

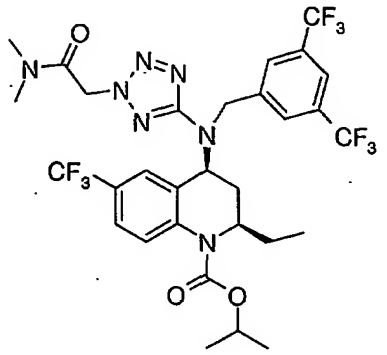
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-carbamoylmethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 5**) by replacing (bromomethyl)cyclopropane with 2-chloroacetamide and heating at 130 °C for 1 h. MS (ES+): 682 (M+H), 704 (M+ Na).

Example 16

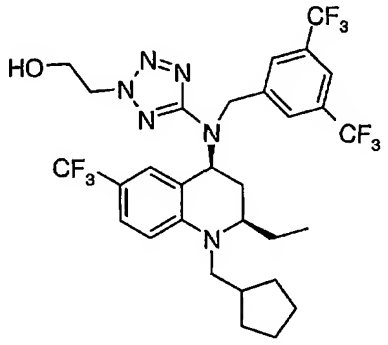
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-dimethylcarbamoylmethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



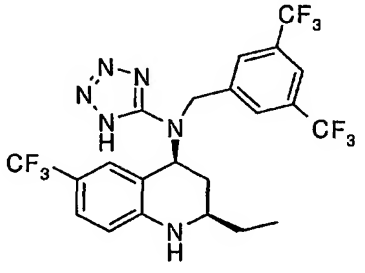
Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 5**) by replacing (bromomethyl)cyclopropane with N,N-dimethylchloroacetamide. MS (ES+): 710 (M+H).

Example 17

Synthesis of (2R,4S)-2-{5-[(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amino]-tetrazol-2-yl}-ethanol

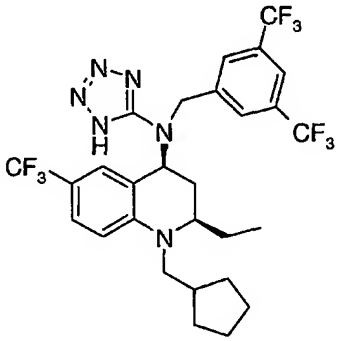


Step 1. Preparation of (2R,4S)-(3,5-Bis-trifluoromethyl-benzyl)-(2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(2-methyl-2H-tetrazol-5-yl)-amine



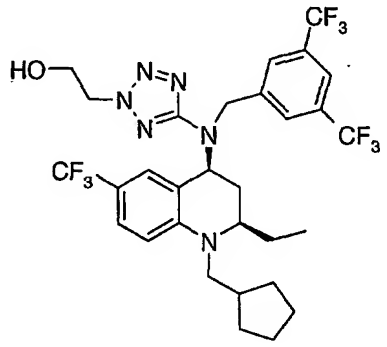
Add trifluoroacetic acid (3 mL) and concentrated sulfuric acid (0.2 mL) to (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1, step 10**) (100 mg, 0.16 mmol). Stir the mixture at room temperature for 2 days. Remove the solvents under reduced pressure. Add saturated aqueous NaHCO3 and dichloromethane. Separate the layers, dry the organic phase over anhydrous magnesium sulfate, filter and remove the solvents under reduced pressure to afford 45 mg (52%) of the title compound. MS (ES+): 539 (M+H).

Step 2. Preparation of (2R,4S)-(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(2H-tetrazol-5-yl)-amine



Add acetic acid (0.43 mL, 7.55 mmol) and cyclopentylcarboxaldehyde (613 mg, 6.25 mmol), to a room temperature solution of (2R,4S)-(3,5-bis-trifluoromethyl-benzyl)-(2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(2-methyl-2H-tetrazol-5-yl)-amine (675 mg, 1.25 mmol). After stirring 30 minutes, add sodium triacetoxyborohydride (1.32 g, 6.25 mmol) and stir at room temperature for two days. Then add cyclopentylcarboxaldehyde (613 mg, 6.25 mmol), acetic acid (0.43 mL, 7.55 mmol) and sodium triacetoxyborohydride (1.32 g, 6.25 mmol) and stir at room temperature for three days. Add saturated aqueous sodium bicarbonate and dichloromethane, separate the layers and dry the organic phase over anhydrous Na2SO4, filter and remove the solvents under vacuum. Chromatograph the residue over silica gel, eluting with hexanes/ethyl acetate to afford the title compound, 155 mg (20%). MS (ES+): 621 (M+H).

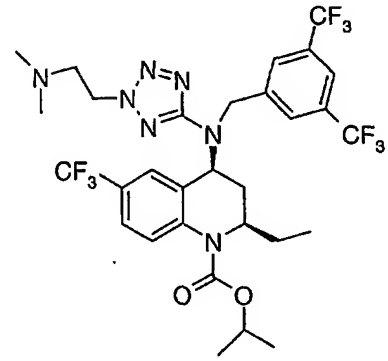
Step 3. Preparation of (2R,4S)-2-{5-[(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amino]-tetrazol-2-yl}-ethanol



Add potassium carbonate (31 mg, 0.227 mmol) and 2-bromoethanol (0.014 mL, 0.20 mmol) to a solution of (2R,4S)-(3,5-bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(2H-tetrazol-5-yl)-amine (83 mg, 0.134 mmol) in dimethylformamide (0.3 mL) at room temperature. Add 2-bromoethanol (0.014 mL, 0.20 mmol) and stir the mixture at 50 °C for two hours. Purify the residue by flash chromatography, eluting with hexane/ethyl acetate, to provide 40 mg (45%) of the title compound. MS (ES+): 667 (M+H).

Example 18

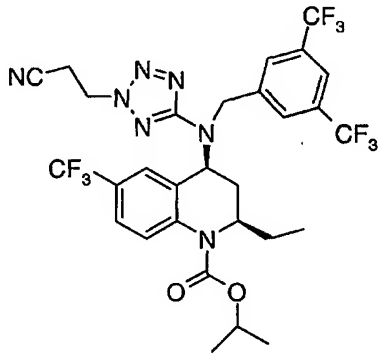
Synthesis of (2R-4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-dimethylamino-ethyl)-2H-tetrazol-5-yl]-amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing 1-propanol with 2-dimethylamino-ethanol in **Example 1, step 11**. MS (ES+): 696 (M+H).

Example 19

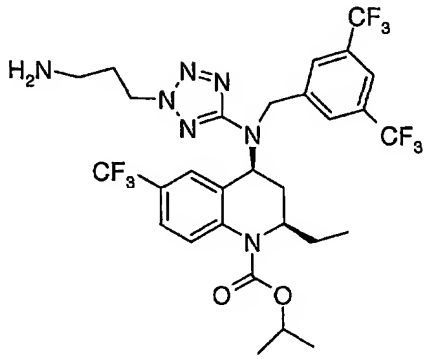
Synthesis of (2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-cyano-ethyl)-2H-tetrazol-5-yl]-amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



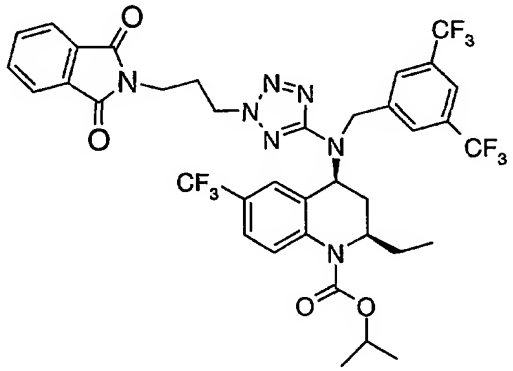
Add acrylonitrile (0.031mL, 0.48 mmol) to a solution of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1, step 10**) (200 mg, 0.32 mmol) and triethylamine (0.045 mL, 0.32 mmol) in acetonitrile (0.5 mL). Stir the mixture at room temperature under nitrogen overnight, then add more acrylonitrile (0.031mL, 0.48 mmol), triethylamine (0.045 mL, 0.32 mmol) and acetonitrile (0.5 mL). Stir the mixture for two days and add more acrylonitrile (0.062 mL, 0.96 mmol) and triethylamine (0.090 mL, 0.64 mmol). Stir the mixture for one day, then evaporate the solvent and purify the crude by chromatography, eluting with hexanes/ethyl acetate (7/3) to afford the title compound (61 mg, 28%). MS (ES+): 678 (M+H).

Example 20

Synthesis of (2R,4S)-4-[[2-(3-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

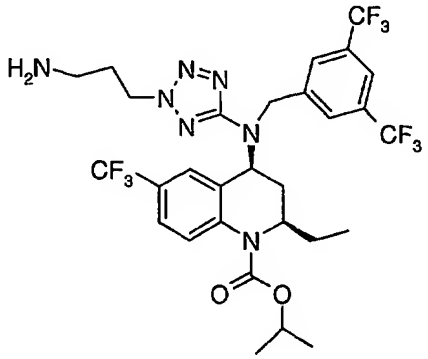


Step 1. Preparation of (2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing 1-propanol with N-(2-hydroxypropyl)-phtalimide in **Example 1, step 11**. MS (ES+): 812 (M+H).

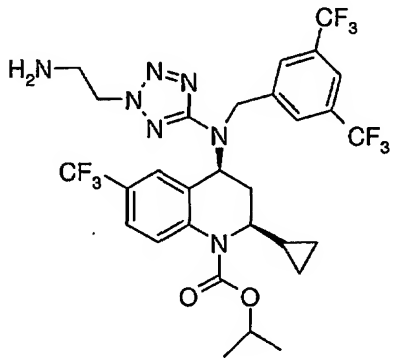
Step 2. Preparation of (2R,4S)-4-[[2-(3-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



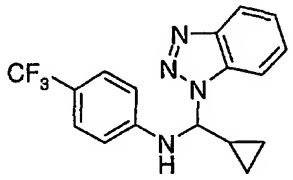
Prepare the title compound by essentially following the procedure described in **Example 4** by replacing (2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester. MS (ES+): 682 (M+H).

Example 21

Synthesis of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

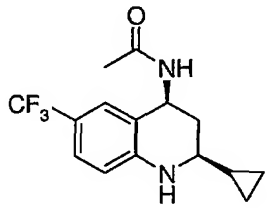


Step 1. Preparation of (Benzotriazol-1-yl-cyclopropyl-methyl)-(4-trifluoromethyl-phenyl)-amine.



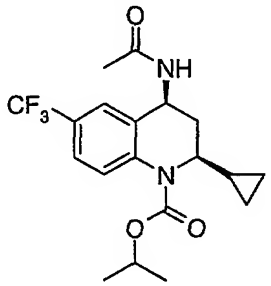
Add a solution of 4-(trifluoromethyl)aniline (2.5 g, 15.4 mmol) in dry toluene (2.5 mL), to a suspension of benzotriazole (1.84 g, 15.4 mmol) in dry toluene (20 mL) at room temperature,under nitrogen atmosphere. Then add a solution of cyclopropane-carbaldehyde (1.26 mL, 16.9 mmol) in dry toluene (2.5 mL) slowly. Stir the reaction mixture at room temperature overnight. Add hexane (25 mL), stir for 1 h and filter the suspension. Wash the resulting solid with hexane and dry under vacuo to afford 3.87 g (76%) of the titled compound. MS (ES+): 333 (M+H).

Step 2. Preparation of (+/-) cis- N-(2-Cyclopropyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide.



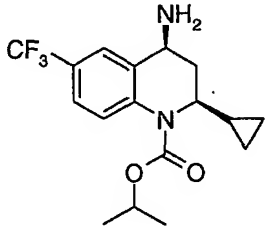
Add N-vinyl acetamide (512 mg, 6.02 mmol) and p-toluenesulfonic acid monohydrate (12 mg, 0.06 mmol) to a suspension of (benzotriazol-1-yl-cyclopropyl-methyl)-(4-trifluoromethyl-phenyl)-amine (2.0 g, 6.02 mmol) in dry toluene (19 mL) at room temperature, under nitrogen atmosphere. Stir the reaction mixture at 70 °C for 2 h. Cool the mixture to room temperature, transfer it to a separatory funnel, add ethyl acetate (20 mL) and 1N NaOH (10 mL). Separate the layers, wash the organic phase with water (10 mL), brine (10 mL) and dry over anhydrous magnesium sulfate, filter and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with hexane/ethyl acetate, to provide 1.39 g (78%) of the title compound. MS (ES+): 299 (M+H).

Step 3. Preparation of (+/-) cis- 4-Acetylamino-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



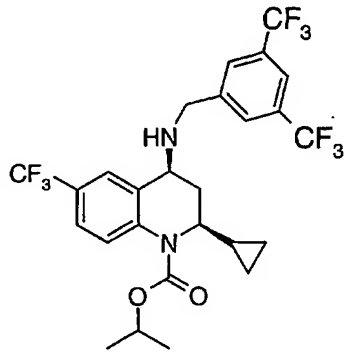
Add isopropyl chloroformate (23.3 mL, 23.3 mmol, 1.0 M in toluene) dropwise to a solution of (+/-) cis- N-(2-cyclopropyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (1.39 mmol, 4.66 mmol) and pyridine (1.9 mL, 23.3 mmol) in dry dichloromethane (32 mL) at 0 °C under nitrogen atmosphere and stir at room temperature overnight. Add 1 N HCl and separate the layers. Extract the aqueous layer with dichloromethane. Dry the organic layers over anhydrous magnesium sulfate, filter, and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with hexane/ethyl acetate, to provide 1.47 g (82%) of the title compound. MS (ES+): 385 (M+H).

Step 4. Preparation of (+/-) cis- 4-amino-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



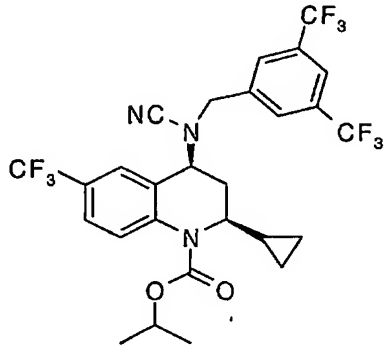
Add 5N HCl (58 mL) to a solution of (+/-) cis- 4-acetylamino-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (1.22 g, 3.17 mmol) in ethanol (24 mL) at 50 °C. Heat the mixture at 100 °C for 12 h. Cool the mixture to room temperature and add sodium carbonate till basic pH and extract with dichloromethane. Separate the layers, dry the organic layers over anhydrous magnesium sulfate, filter, and remove the solvent under reduced pressure. Purify the residue by SCX cartridge to provide 814 mg (75%) of the title compound. MS (ES+): 343 (M+H).

Step 5. Preparation of (+/-) cis- 4-(3,5-Bis-trifluoromethyl-benzylamino)-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



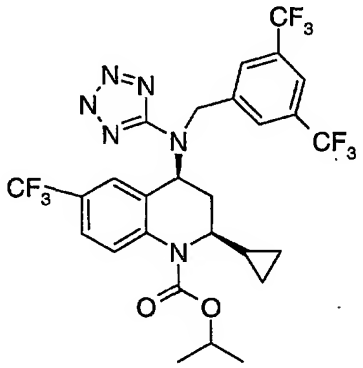
Add sodium triacetoxyborohydride (753 mg, 3.56 mmol) to a mixture 3,5-Bis-trifluoromethyl-benzaldehyde (0.390 mL, 2.37 mmol), acetic acid (0.136 mL, 2.37 mmol) and (+/-) cis- 4-amino-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (810 mg, 2.37 mmol) in dichloroethane (8.4 mL). Stir the mixture at room temperature under nitrogen atmosphere overnight. Add saturated sodium bicarbonate, separate the layers and extract the aqueous phase with dichloromethane. Dry the organic layers over anhydrous magnesium sulfate, filter, and remove the solvent under reduced pressure. Purify the residue by flash chromatography, eluting with hexane/ethyl acetate, to provide 804 mg (60%) of the title compound. MS (ES+): 569 (M+H).

Step 6. Preparation of (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-cyano-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



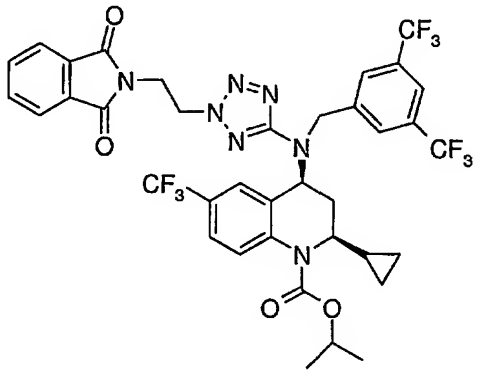
Add cyanogen bromide (603 mg, 5.64 mmol) and potassium tert-butoxyde (334 mg, 2.82 mmol) to a solution of (+/-) cis- 4-(3,5-Bis-trifluoromethyl-benzylamino)-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (804 mg, 1.41 mmol) at room temperature. Stir the mixture at room temperature under nitrogen atmosphere overnight. Then add cyanogen bromide (301 mg, 2.82 mmol) and potassium tert-butoxyde (167 mg, 1.41 mmol) and stir overnight. Add water and ethyl acetate. Separate the layers and wash the organic layers with water and brine. Dry the organic phase over anhydrous magnesium sulfate, filter and remove the solvents under vacuum. Purify the residue by flash chromatography, eluting with hexanes/ethyl acetate to afford the titled compound (458 mg, 55%). MS (ES+): 594 (M+H).

Step 7. Preparation of (+/-) cis- 4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



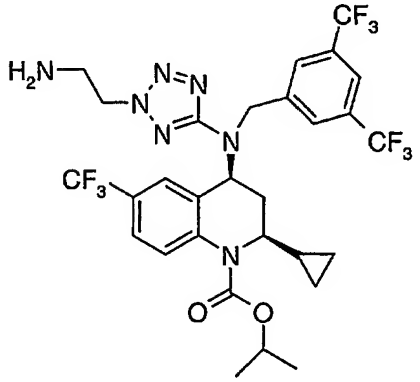
Add sodium azide (150 mg, 2.30 mmol) and triethylamine hydrochloride (317 mg, 2.30 mmol) to a solution of (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-cyano-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (455 mg, 0.77 mmol) in dry toluene (15.3 mL). Heat the mixture at 100 °C overnight. Cool down the mixture to room temperature, add dichloromethane and 1 M hydrochloric acid. Separate the layers and extract the aqueous layer with dichloromethane. Wash the organic phase with brine, dry over anhydrous magnesium sulfate, filter and remove the solvent under reduced pressure to provide 457 mg (93%). MS (ES-): 635 (M-H).

Step 8. Preparation of (+/-)-cis 4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure set forth in preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and 1-propanol with N-(2-hydroxyethyl)-phtalimide in **Example 1, step 11**. MS (ES+): 810 (M+H).

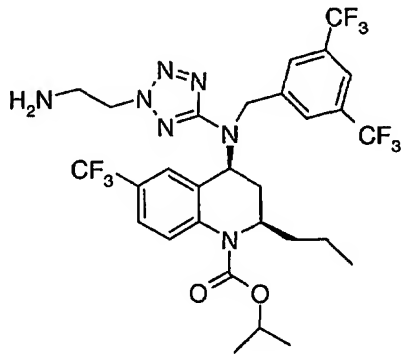
Step 9. Preparation of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Add a 40% solution of methylamine in water (0.226 mL) to a solution of (+/-)-cis 4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (70 mg, 0.86 mmol) in ethanol (0.453 mL). Heat the mixture at 40 °C and stir overnight. Cool down to room temperature, then remove the solvent under reduced pressure. Add ether and 1 N HCl, separate the layers, wash the organic phase with a saturated solution of $NaHCO_3$, dry over anhydrous magnesium sulfate, filter and remove the solvent under reduced pressure to afford the title compound 52 mg (90%). MS (ES+): 682 (M+H).

Example 22

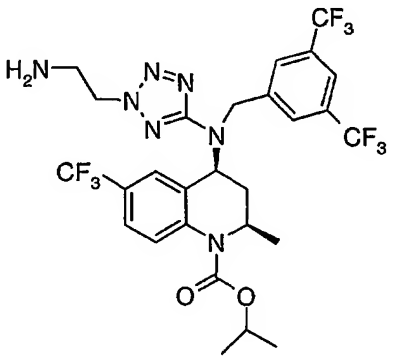
Synthesis of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-propyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



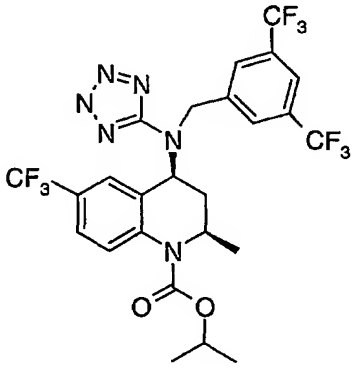
Prepare the title compound by essentially following the procedure set forth in preparation of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 21**) by replacing cyclopropanecarbaldehyde with butyraldehyde in **Example 21, step 1**. MS (ES+): 684 (M+H).

Example 23

Synthesis of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

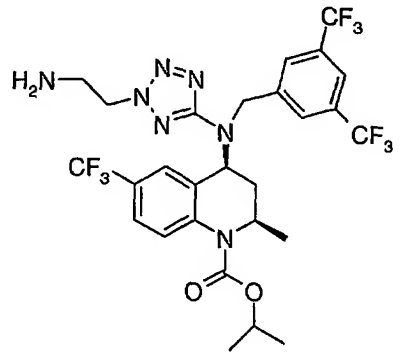


Step 1. Preparation of (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure set forth in the preparation of (+/-) cis- 4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 21, step 7**) by replacing cyclopropanecarbaldehyde with acetaldehyde in **Example 21, step 1**. MS (ES-): 609 (M-H).

Step 2. Preparation of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

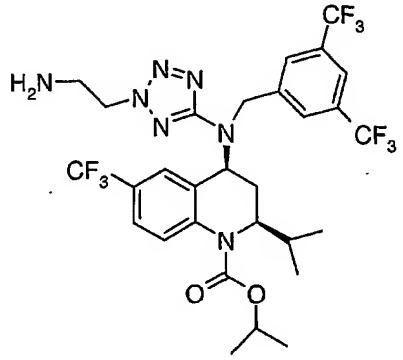


Prepare the title compound by essentially following the procedure set forth in preparation of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 21**) by replacing (+/-) cis- 4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester in **Example 21, step 8.**

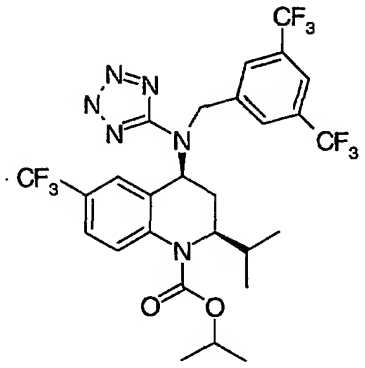
MS (ES+): 654 (M+H).

Example 24

Synthesis of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

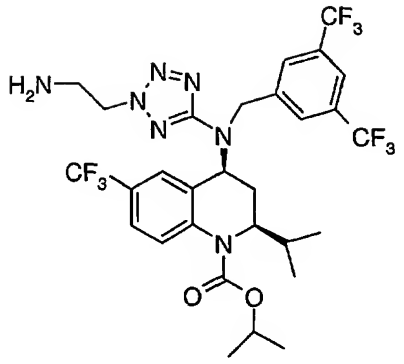


Step 1. Preparation of (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure set forth in the preparation of (+/-) cis- 4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 21, step 7**) by replacing cyclopropanecarbaldehyde with isobutyraldehyde in **Example 21, step 1**. MS (ES-): 637 (M-H).

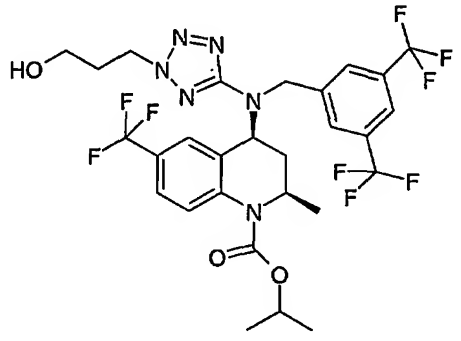
Step 2. Preparation of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure set forth in preparation of (+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 21**) by replacing (+/-) cis- 4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester in **Example 21, step 8**. MS (ES+): 682 (M+H).

Example 25

Synthesis of (+/-)-cis 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

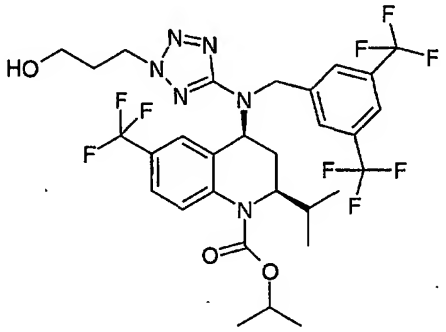


Prepare the title compound by essentially following the procedure set forth in preparation (2R,4S)-2-{5-[(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amino]-tetrazol-2-yl}-ethanol

(**Example 17**) by replacing (2R,4S)-(3,5-bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(2H-tetrazol-5-yl)-amine with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 2-bromoethanol with 3-bromopropanol in **Example 17, step 3**. MS (ES+): 669 (M+H).

Example 26

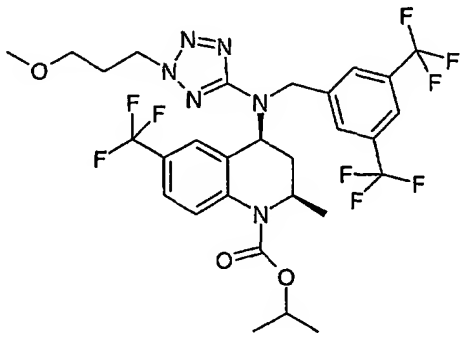
Synthesis of (+/-)-cis-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl]-amino}-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure set forth in the preparation of(2R,4S)-2-{5-[(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amino]-tetrazol-2-yl}-ethanol (**Example 17**) by replacing (2R,4S)-(3,5-bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(2H-tetrazol-5-yl)-amine with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 24, step 1**) and 2-bromoethanol with 3-bromopropanol in **Example 17, step 3**. MS (ES+): 697 (M+H).

Example 27

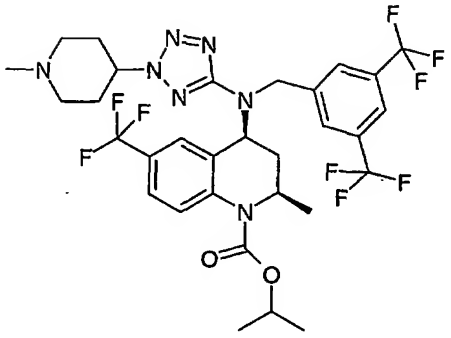
Synthesis of (+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-methoxy-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 3-methoxy-propan-1-ol in **Example 1, step 11**. MS (ES+): 683 (M+H).

Example 28

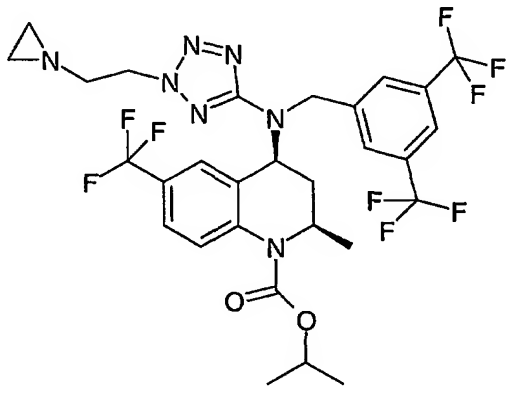
Synthesis of (+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-piperidin-4-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 1-methyl-piperidin-4-ol in **Example 1, step 11**. MS (ES+): 708 (M+H).

Example 29

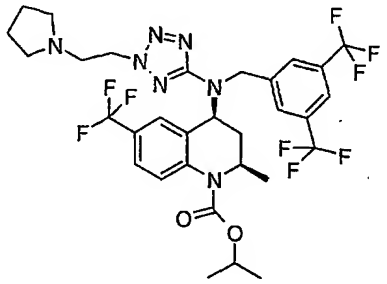
Synthesis of (+/-)-cis- 4-[[2-(2-Aziridin-1-yl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 2-aziridin-1-yl-ethanol in **Example 1, step 11**. MS (ES+): 680 (M+H).

Example 30

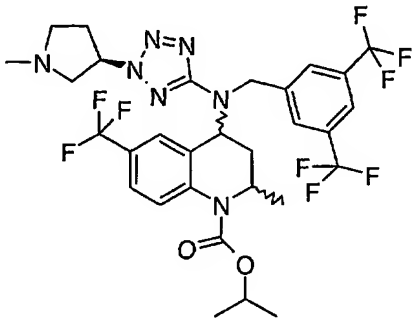
Synthesis of (+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-pyrrolidin-1-yl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 2-pyrrolidin-1-yl-ethanol in **Example 1, step 11**. MS (ES+): 708 (M+H).

Example 31

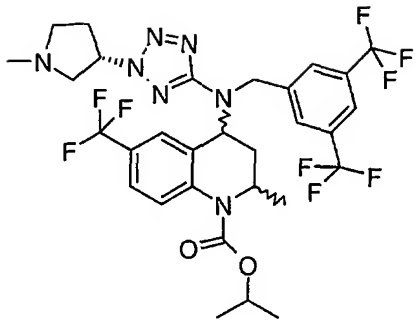
Synthesis of (2*R*,4*S*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3*R*-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3*R*-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compounds as a mixture by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 1-methyl-pyrrolidin-3*R*-ol in **Example 1, step 11**. MS (ES+): 694 (M+H).

Example 32

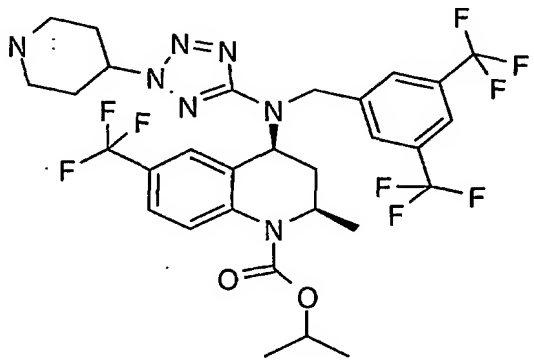
Synthesis of (2*R*,4*S*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3*S*-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3*S*-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



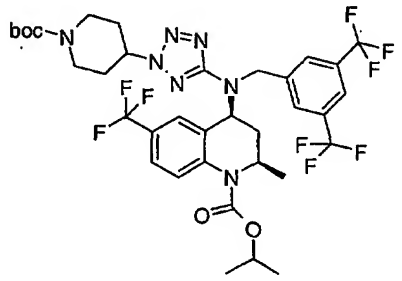
Prepare the title compounds as a mixture by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 1-methyl-pyrrolidin-3*S*-ol in **Example 1, step 11**. MS (ES+): 694 (M+H).

Example 33

Synthesis of (+/-)-cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-piperidin-4-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

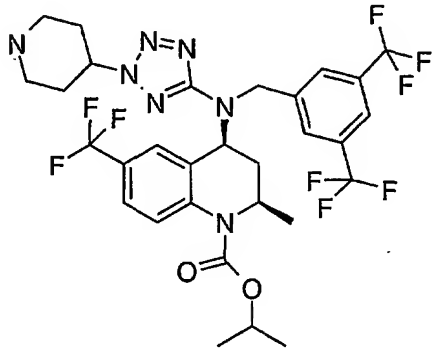


Step 1. Preparation of (+/-)-cis-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester in **Example 1, step 11**. MS (ES+): 694 (M+H-boc).

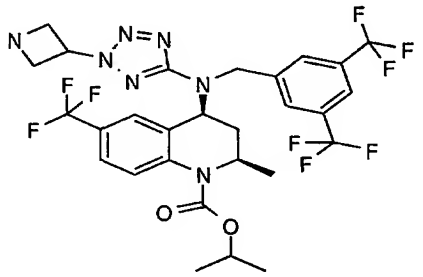
Step 2. Preparation of (+/-)-cis-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-piperidin-4-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



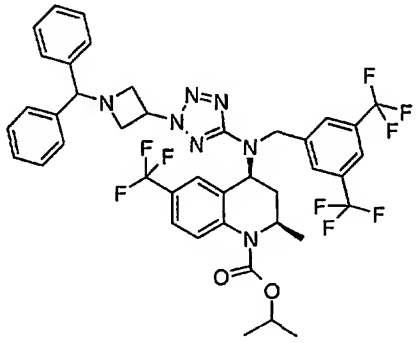
Add trifluoroacetic acid (0.5 mL) to a solution of (+/-)-cis-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-tert-butoxycarbonyl-piperidin-4-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (156 mg, 0.20 mmol) in dichloromethane (0.5 mL). Stir the mixture at room temperature for 1 h. Evaporate the volatiles and purify the residue with a SCX cartridge. Elution with MeOH with 2 M ammonia afforded the title compound (121 mg, 87%). MS (ES+): 694 (M+H).

Example 34

Synthesis of (+/-)-cis- 4-[(2-Azetidin-3-yl-2H-tetrazol-5-yl)-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

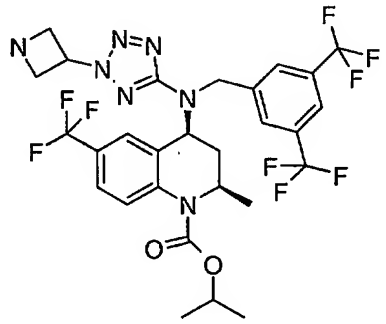


Step 1. Preparation of (+/-)-cis- 4-[[2-(1-Benzhydryl-azetidin-3-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compound by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 1-benzhydryl-azetidin-3-ol in **Example 1, step 11**. MS (ES+): 850 (M+18).

Step 2. Preparation of (+/-)-cis-4-[(2-Azetidin-3-yl-2H-tetrazol-5-yl)-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

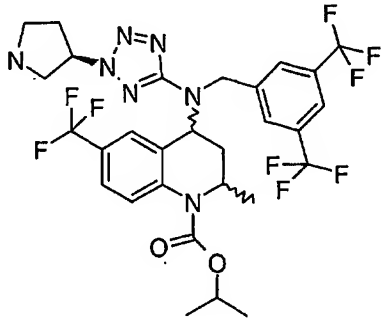


Stir a mixture of (+/-)-cis- 4-[[2-(1-Benzhydryl-azetidin-3-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (40 mg, 0.048 mmol) and Pd/C 10% (5 mg) in methanol (1 mL) under hydrogen atmosphere for 2 h. Filter the solid, wash with dichloromethane. Evaporate the solvent and purify the residue with a silica cartridge (elution with dichlormethane/methanol with 2 M ammonia to afford the title compound (25 mg, 78%). MS (ES+): 684 (M+18).

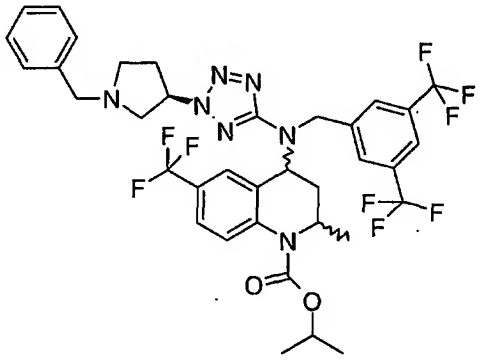
Example 35

Synthesis of (2*R*,4*S*)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*R*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic

acid isopropyl ester and (2*S*,4*R*)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*R*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



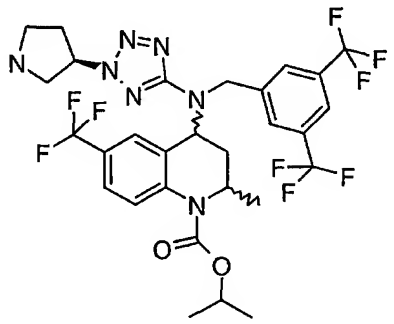
Step 1. Preparation of (2*R*,4*S*)-4-[[2-(1-Benzyl-pyrrolidin-3*R*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(1-Benzyl-pyrrolidin-3*R*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compounds as a mixture by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl

ester (**Example 23, step 1**) and 1-propanol with 1-benzyl-pyrrolidin-3*R*-ol in **Example 1, step 11**. MS (ES+): 770 (M+H).

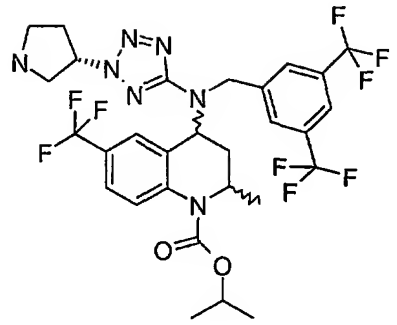
Step 2. Preparation of (2*R*,4*S*)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*R*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*R*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



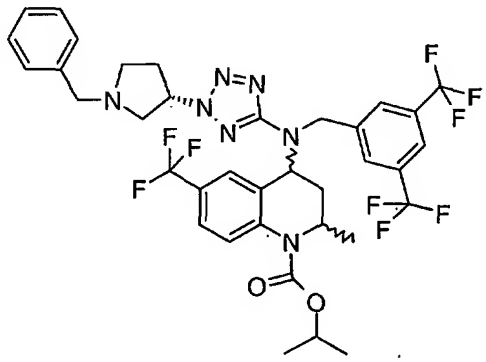
Stir a mixture of 2*R*,4*S*)-4-[[2-(1-Benzyl-pyrrolidin-3*R*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(1-Benzyl-pyrrolidin-3*R*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (227 mg, 0.29 mmol) and Pd/C 10% (30 mg) in methanol (3 mL) under hydrogen atmosphere for 2 h. Filter the solid, wash with dichloromethane. Evaporate the solvent and purify the residue with a silica cartridge (elution with dichloromethane/methanol with 2 M ammonia to afford the title compounds (180 mg, 89%). MS (ES+): 680 (M+H).

Example 36

Synthesis of (2*R*,4*S*)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*S*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*S*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.

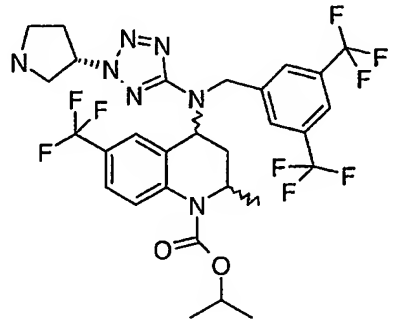


Step 1. Preparation of (2*R*,4*S*)-4-[[2-(1-Benzyl-pyrrolidin-3*S*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(1-Benzyl-pyrrolidin-3*S*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Prepare the title compounds as a mixture by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with 1-benzyl-pyrrolidin-3*S*-ol in **Example 1, step 11**. MS (ES+): 770 (M+H).

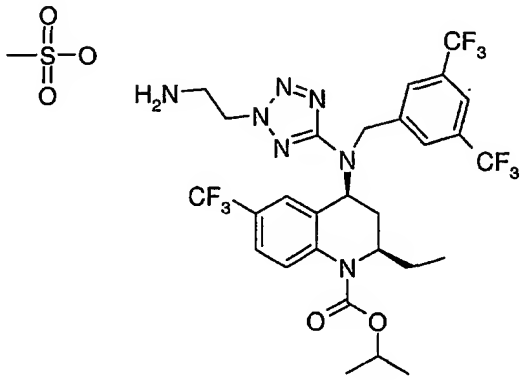
Step 2. Preparation of (2*R*,4*S*)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*S*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3*S*-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester.



Stir a mixture of (2*R*,4*S*)-4-[[2-(1-Benzyl-pyrrolidin-3*S*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(1-Benzyl-pyrrolidin-3*S*-yl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (229 mg, 0.30 mmol) and Pd/C 10% (30 mg) in methanol (3 mL) under hydrogen atmosphere for 2 h. Filter the solid, wash with dichloromethane. Evaporate the solvent and purify the residue with a SCX cartridge (elution with methanol with 2 M ammonia) to afford the title compounds (182 mg, 91%). MS (ES+): 680 (M+H).

Example 37

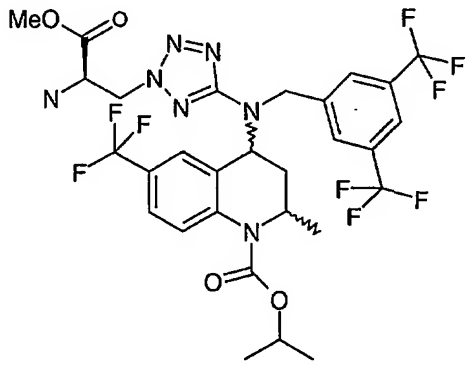
Synthesis of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester methanesulfonic acid salt.



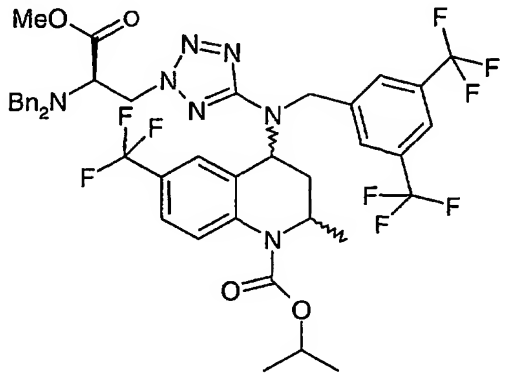
Add a solution of methanesufonic acid 1 M in dichloromethane/methanol (95/5) (0.088mL, 0.088 mmol) to a solution of (2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 4**) (60 mg, 0.088 mmol) in dichloromethane/methanol (95/5) (0.52 mL). Stir the mixture 5 min at room temperature. Remove the volatiles under reduced pressure. Wash the solid with hexane and dry to afford the title compound (68 mg, 100%). MS (ES+): 668 (M free base+H).

Example 38

Synthesis of (2*R*,4*S*)-4-[[2-(2*R*-Amino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(2*R*-Amino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester

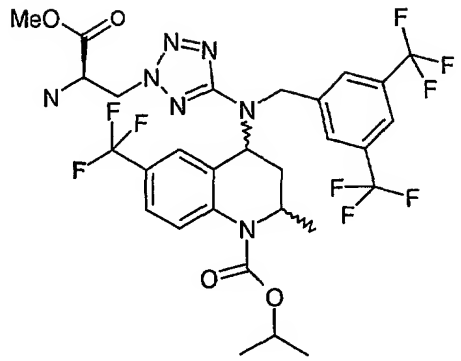


Step 1. Preparation of (2*R*,4*S*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2 *R*-dibenzylamino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2 *R*-dibenzylamino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



Prepare the title compounds as a mixture by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 23, step 1**) and 1-propanol with (S)-2-dibenzylamino-3-hydroxypropionic acid methyl ester in **Example 1, step 11**. MS (ES+): 892 (M+H).

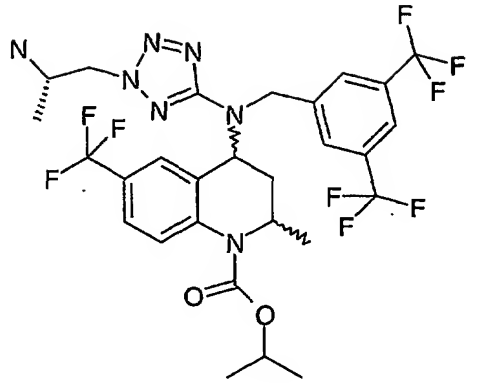
Step 2. Preparation of (2*R*,4*S*)-4-[[2-(2*R*-Amino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(2*R*-Amino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



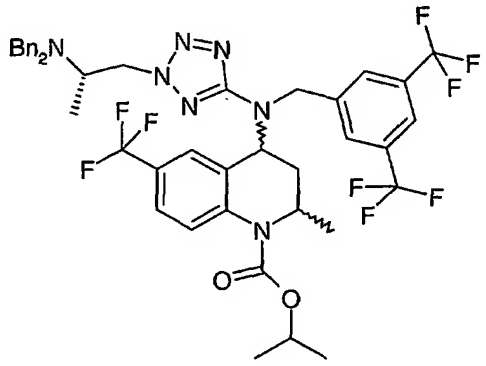
Stir a mixture of (2*R*,4*S*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2 *R*-dibenzylamino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2 *R*-dibenzylamino-2-methoxycarbonyl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (143 mg, 0.16 mmol) and Pd/C 10% (16 mg) in methanol (1.6 mL) under hydrogen atmosphere overnight. Add more Pd/C 10% (15 mg) and stir for 72 h. Filter the solid, wash with dichloromethane. Evaporate the solvent and purify the residue with silica amino cartridge (elution with hexane/ethanol) to afford the title compounds (39 mg, 34%). MS (ES+): 712 (M+H).

Example 39

Synthesis of (2*R*,4*S*)-4-[[2-(2*S*-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(2*S*-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



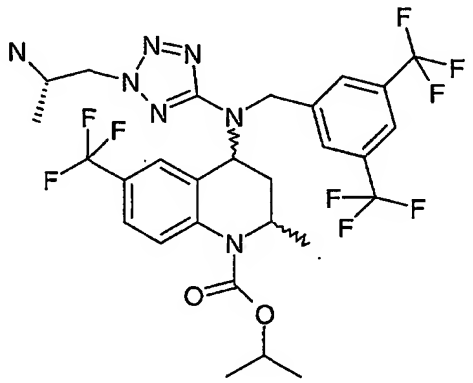
Step 1. Preparation of (2*R*,4*S*)- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2*S*-dibenzylamino-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2*S*-dibenzylamino-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



Prepare the title compounds as a mixture by essentially following the procedure described for the preparation of (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (**Example 1**) by replacing (2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(1H-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester with (+/-) cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl

ester (**Example 23, step 1**) and 1-propanol with 2*S*-dibenzylamino-propan-1-ol in **Example 1, step 11**. MS (ES+): 848 (M+H).

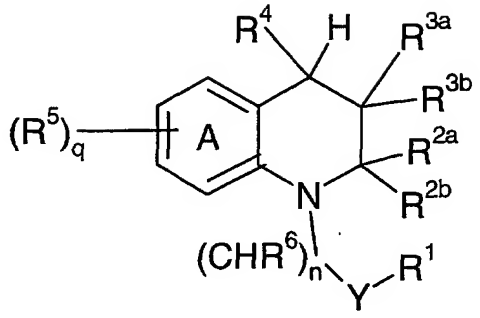
Step 2. Preparation of (2*R*,4*S*)-4-[[2-(2*S*-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)-4-[[2-(2*S*-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester



Stir a mixture of (2*R*,4*S*)- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2*S*-dibenzylamino-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester and (2*S*,4*R*)- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2*S*-dibenzylamino-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester (128 mg, 0.15 mmol) and Pd/C 10% (15 mg) in methanol (1.5 mL) under hydrogen atmosphere overnight. Add more Pd/C 10% (15 mg) and stir for 72 h. Filter the solid, wash with dichloromethane. Evaporate the solvent and purify the residue with silica amino cartridge (elution with hexane/ethanol) to afford the title compounds (57 mg, 57%). MS (ES+): 668 (M+H).

We claim:

1. A compound of Formula I



I

wherein

n is 0, 1, 2, or 3;

q is 0, 1, 2, 3, or 4;

Y is a bond, C=O, or -$S(O)_t$; wherein t is 0, 1, or 2;

R^1 is selected from a group consisting of: hydroxy, C_1-C_6 alkyl, aryl, C_2-C_6 alkenyl, C_1-C_6 haloalkyl, C_1-C_6 alkylheterocyclic, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl; C_1-C_6 alkylaryl, heterocyclyl, C_1-C_6 alkylalcohol, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, -OC_1-C_6 alkylheterocyclic, -OC_3-C_8 cycloalkyl, -OC_1-C_6 alkylcycloalkyl, -NR^7R^8 and -OC_1-C_6 alkylaryl, -O-heterocyclic, -OC_1-C_6 alkylheterocyclic, C_1-C_6 alkyl-O-$C(O)NR^7R^8$, C_1-C_6 alkyl-$NR^7C(O)NR^7R^8$, and C_0-C_6 alkyl$COOR^{11}$; provided that R^1 is not hydroxy when Y is -$S(O)_t$; and wherein each cycloalkyl, aryl and heterocyclic group is optionally substituted with 1 to 3 groups independently selected from oxo, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, C_1-C_6 alkylalcohol, $CONR^{11}R^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{11}COR^{12}$, C_0-C_3 alkyl$NR^{11}R^{12}$, C_1-C_3 alkylCOR^{11}, C_0-C_6 alkyl$COOR^{11}$, cyano, C_1-C_6 alkylcycloalkyl, phenyl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylaryl, -OC_1-C_6 alkylheterocyclic, and C_1-C_6 alkylaryl;

R^{2a} and R^{2b} are each independently selected from the group consisting of: hydrogen, hydroxy, halo, oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, $CONR^{11}R^{12}$, -$NR^{11}SO_2R^{12}$, -$NR^{11}COR^{12}$, C_0-C_6 alkyl$NR^{11}R^{12}$, C_0-C_6

alkylCOR^{11}, C_0-C_6 alkylCOOR^{11}, cyano, nitro, C_0-C_6 alkylcycloalkyl, phenyl, C_0-C_6 alkylaryl, heterocyclyl, C_3-C_8 cycloalkyl, and C_1-C_6 haloalkyl; provided that both R^{2a} and R^{2b} are not simultaneously hydrogen;

R^{3a} and R^{3b} are independently selected from the group consisting of: hydrogen, halo, C_1-C_6 alkyl, C_2-C_6 alkene, C_2-C_6 alkynyl, C_1-C_6 alkoxy, and C_1-C_6 haloalkyl;

R^4 is a group represented by the formula -NR^{4a}R^{4b} where;

R^{4a} is a heterocyclic group substituted with 1 to 3 groups independently selected from C_3-C_6 alkyl, C_3-C_6 alkenyl, C_0-C_6 alkylCN, C_3-C_6 alkoxy, C_1-C_6 alkylalcohol, C_3-C_6 haloalkyl, -OC(O)NR^{11}R^{12}, C_1-C_6 alkylNR^{11}R^{12} wherein the C_1-C_6 alkyl group is optionally substituted with -OR^{10} or C(O) OR^{10}, C_0-C_6 alkylNR^{11}SO$_2$R^{12}, C_0-C_6 alkylC(O)NR^{11}R^{12}, C_0-C_6 alkylNR^{11}C(O)R^{12}, C_0-C_6 alkylNR^{11}C(O)OR^{12}, C_0-C_6 alkylNR^{11}CHR^{10}CO$_2$R^{12}, C_0-C_6 alkylC(O)OR^{11}, C_0-C_6 alkylSO$_2$NR^{11}R^{12}, C_0-C_6 alkylS(O)$_t$R^{11}, C_3-C_8 cycloalkyl, C_1-C_6 alkylcycloalkyl, and C_0-C_6 alkylheterocyclic wherein the heterocycle of the C_0-C_6 alkylheterocyclic group is optionally substituted with halo, C_1-C_6 alkyl, oxo, -CO$_2$R^{11} and -NR^{11}R^{12}; and

R^{4b} is selected from the group consisting of C_1-C_6 alkylaryl, C_2-C_6 alkenylaryl, C_2-C_6 alkynylaryl, C_1-C_6 alkylheterocyclic, C_2-C_6 alkenylheterocyclic, C_1-C_6 alkylcycloalkyl, and C_1-C_6 alkyl-O-C_1-C_6 alkylaryl, wherein each cycloalkyl, aryl, or heterocyclic group is optionally substituted with 1-3 groups independently selected from the group consisting of hydroxy, oxo, -SC_1-C_6 alkyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 haloalkyl, halogen, C_1-C_6 alkoxy, aryloxy, C_1-C_6 alkenyloxy, C_1-C_6 haloalkoxyalkyl, C_0-C_6 alkylNR^{11}R^{12}, -OC_1-C_6 alkylaryl, nitro, cyano, C_1-C_6 haloalkylalcohol, and C_1-C_6 alkyl alcohol;

R^5 is selected from a group consisting of: hydrogen, hydroxy, halo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_1-C_6 haloalkyl, C_3-C_8 cycloalkyl, C_1-C_6 alkylaryl, C_1-C_6 alkylheterocyclic, C_2-C_6 alkenylaryl, C_2-C_6 alkenylheterocyclic, aryl, heterocyclic, cyano, nitro, C_0-C_6 alkylNR^{7}R^8, C_0-C_6 alkylCOR^7, C_0-C_6 alkylCO$_2$R^7, C_0-C_6 alkylCONR^{7}R^8, CONR^{7}SO$_2$R^8, -NR^{7}SO$_2$R^8, -NR^{7}COR^8, -N=CR^{7}R^8, OCONR^{7}R^8, -S(O)$_t$R^7, -SO$_2$NR^{7}R^8, C_0-C_5CH$_2$OH, -OC_1-C_6 alkylheterocyclic, and -OC_1-C_6 alkylaryl wherein each of the alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heterocyclic group or subgroup is optionally substituted with oxo, alkyloxy, aryloxy; and wherein any two R^5 groups may combine to form an

optionally substituted 5, 6, or 7-member fused ring with the phenyl ring (A-ring) to which they are attached, wherein the 5, 6, or 7-member fused ring is saturated, partially unsaturated, or fully unsaturated and optionally contains 1, 2, or 3 heteroatoms independently selected from O, N, and S;

R^6 is independently selected from a group consisting of hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, hydrthanks

oxy, COR^7, C_1-C_6 alkoxy, aryloxy, -OC_2-C_6 alkenyl, -OC_1-C_6 haloalkyl, C_1-C_6 alkylNR^7R^8, C_3-C_8 cycloalkyl, heterocyclic, aryl, C_1-C_6 alkyl-O-C(O)NR^7R^8, C_1-C_6 alkyl-$NR^7C(O)NR^7R^8$ and C_1-C_6 alkylcycloalkyl;

R^7 and R^8 are each independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -OC_1-C_6 alkyl, C_1-C_6 haloalkyl, -O-aryl, -OC_3-C_8 cycloalkyl, -O-heterocyclic, -NR^7R^8, -C_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylcycloalkyl, -OC_1-C_6 alkylheterocyclic, C_1-C_6 alkylheterocyclic, -OC_1-C_6 alkylaryl, C_3-C_8 cycloalkyl, heterocyclic, aryl, and C_1-C_6 alkylaryl, wherein each alkyl, cycloalkyl, heterocyclic or aryl group is optionally substituted with 1-3 groups independently selected from hydroxy, CN, halo, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkyl, and $NR^{11}R^{12}$, or R^7 and R^8 combine to form a nitrogen containing heterocyclic ring which having 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen and sulfur and wherein the nitrogen-containing heterocycle is optionally substituted with oxo, or C_1-C_6 alkyl;

R^{10}, R^{11}, and R^{12} are each independently selected from a group consisting of: hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_8 cycloalkyl, heterocyclic, aryl, C_1-C_6 alkylaryl, wherein each alkyl, aryl, cycloalkyl, and heterocyclic group is optionally substituted with 1-3 groups independently selected from halogen, C_1-C_6 alkylheterocyclic, and C_1-C_6 haloalkyl, or R^{11} and R^{12} combine to form a nitrogen containing heterocyclic ring which may have 0, 1, or 2 additional heteroatoms selected from oxygen, nitrogen or sulfur and is optionally substituted with oxo, C_1-C_6 alkyl, COR^7, and -SO_2R^7;

or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

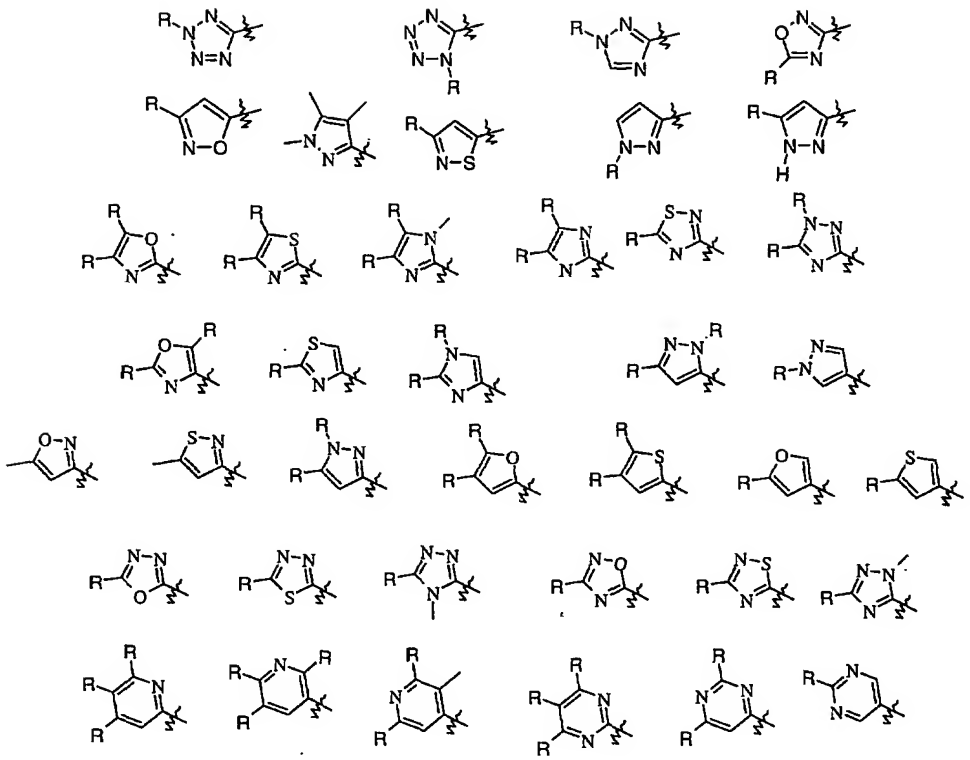
2. A compound according to claim 1 wherein n and q are independently 0 or 1.

3. A compound according to claim 1 or 2 where n is 0, Y is C(O), and R^1 is selected from a group consisting of: hydroxy, -Oaryl, -OC_1-C_6 haloalkyl, -OC_1-C_6 alkylcycloalkyl, -OC_3-C_8 cycloalkyl , -OC_1-C_6 alkylcycloalkylNR^7R^8, -OC_1-C_6 alkyl, -OC_0-C_6 alkylaryl, -OC_1-C_6 alkylcyano, -OC_1-C_6 alkylCO_2R^{11}, -OC_3-C_8 cycloalkylCO_2R^{11}, -OC_1-C_6 alkylhydroxy, -OC_1-C_6 alkylNR^7R^8, and –OC_0-C_6 alkylheterocyclic; and wherein each alkyl, cycloalkyl, aryl, or heterocyclic is optionally substituted with 1 or 2 groups selected from halo, C_0-C_3 alkylalcohol, C_0-C_3 alkylamine, C_0-C_3 alkylCOOH, C_0-C_3alkyl$CONH_2$, C_0-C_3alkylcyano, and C_0-C_3 alkyl$C(O)OC_1$-C_3 alkyl.

4. A compound according to claim 1 wherein R^2 is C_3-C_8 cycloalkyl or C_1-C_6 alkyl.

5. A compound according to claim 1 or 2 wherein n is 0, Y is a bond, and R^1 is selected from a group consisting of: C_1-C_6 alkyl, C_0-C_6 alkylcycloalkyl, C_1-C_6 alkylheterocyclic, C_2-C_6 haloalkyl, C_0-C_6 alkylaryl, C_1-C_6 alkylcycloalkylNR^7R^8, C_1-C_6 alkylcyano, C_1-C_6 alkylCO_2R^{11}, C_1-C_6 alkylcycloalkylCO_2R^{11}, C_1-C_6alkylalcohol, and C_1-C_6 alkylNR^7R^8; and wherein each alkyl, cycloalkyl, aryl, or heterocyclic is optionally substituted with 1 or 2 groups selected from halo, C_0-C_3 alkylalcohol, C_0-C_3 alkylamine, C_0-C_3 alkylCOOH, C_0-C_3 alkyl$CONH_2$, and C_0-C_3 alkylcyano.

6. A compound according to claim 1 wherein R^{3a} and R^{3b} are both hydrogen and R^4 is $NR^{4a}R^{4b}$; wherein R^{4b} is 3,5-bistrifluoromethylbenzyl and R^{4a} is selected from the group consisting of:



wherein, R is independently selected from the group consisting of: C_3-C_6 alkyl, C_1-C_6 alkylalcohol, C_3-C_6 alkoxy, C_0-C_6 alkylcycloalkyl, C_0-C_6 alkylheterocyclic, C_1-C_6 alkylCN, C_3-C_6 haloalkyl, C_0-C_6 alkyl$NR^{11}R^{12}$, C_1-C_6 alkyl$C(O)NR^{11}R^{12}$, and C_1-C_6 alkyl$C(O)OR^{11}$.

7. A compound selected from the group consisting of:

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-propyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyanomethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-((3,5-Bis-trifluoromethyl-benzyl)-{2-[2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-2H-tetrazol-5-yl}-amino)-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-cyclopropylmethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-methoxycarbonylmethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-carboxymethyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-isopropyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-isobutyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-butyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[(3,5-bistrifluoromethylbenzyl)-(2-*tert*-butyl-2*H*-tetrazol-5-yl)amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-hydroxy-ethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(3-hydroxy-propyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-chloro-ethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-carbamoylmethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-dimethylcarbamoylmethyl)-2*H*-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2*H*-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-2-{5-[(3,5-Bis-trifluoromethyl-benzyl)-(1-cyclopentylmethyl-2-ethyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-amino]-tetrazol-2-yl}-ethanol,

(2R-4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-dimethylamino-ethyl)-2H-tetrazol-5-yl]-amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-cyano-ethyl)-2H-tetrazol-5-yl]-amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-[[2-(3-Amino-propyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-cyclopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-propyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-[[2-(2-Amino-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-hydroxy-propyl)-2H-tetrazol-5-yl]-amino}-2-isopropyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(3-methoxy-propyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-piperidin-4-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-[[2-(2-Aziridin-1-yl-ethyl)-2H-tetrazol-5-yl]-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(2-pyrrolidin-1-yl-ethyl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3R-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3R-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3S-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-{(3,5-Bis-trifluoromethyl-benzyl)-[2-(1-methyl-pyrrolidin-3S-yl)-2H-tetrazol-5-yl]-amino}-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-piperidin-4-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(+/-)-cis- 4-[(2-Azetidin-3-yl-2H-tetrazol-5-yl)-(3,5-bis-trifluoromethyl-benzyl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3R-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3R-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)- 4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3S-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2S,4R)-4-[(3,5-Bis-trifluoromethyl-benzyl)-(2-pyrrolidin-3S-yl-2H-tetrazol-5-yl)-amino]-2-methyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester,

(2R,4S)-4-{(3,5-bistrifluoromethylbenzyl)-[2-(2-amino-ethyl)-2H-tetrazol-5-yl)]amino}-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid isopropyl ester methanesulfonic acid salt, and pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof.

8. A method of modulating CETP activity comprising administering a therapeutically effective composition comprising a compound of Formula I, or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer or mixture of diastereomers thereof to a patient in need thereof.

9. The method of medulating CETP activity of claim 8, wherein the modulation of CETP activity results in a decrease in LDL-cholesterol.

10. A method of treating or preventing dyslipidemia comprising administering a therapeutically effective composition comprising a compound of Formula I, or a pharmaceutically acceptable salt, solvate, enantiomer, racemate diastereomer, mixture of diastereomers thereof, to a patient in need thereof.

11. A method of treating or preventing atherosclerosis comprising administering a therapeutically effective composition comprising a compound of Formula I, or a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient.

12. A method of lowering plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of Formula I, or a

pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient in need thereof.

13. A method of treating and/or preventing the pathological sequelae due to high levels of plasma LDL-cholesterol in a mammal comprising administering a therapeutically effective dose of a compound of Formula I, pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers to a patient in need thereof.

14. A pharmaceutical composition comprising a compound according to claim 1 and at least one of: a carrier, diluent and excipient.

15. Use of a compound according to claim 1 for the manufacture of a medicament for treating and/or preventing atherosclerosis in a mammal comprising administering an effective dose of a compound of Formula I, a pharmaceutically acceptable salt, solvate, enantiomer, racemate, diastereomer, or mixture of diastereomers thereof to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/021789

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 C07D401/14 A61K31/4709 A61P3/00 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/17165 A (PFIZER PRODUCTS INC; DENINNO, MICHAEL, PAUL; MAGNUS-ARYITEY, GEORGE, T) 30 March 2000 (2000-03-30) cited in the application claims 1,33-49 example 79	1-15
A	US 2004/204450 A1 (BECHLE BRUCE M ET AL) 14 October 2004 (2004-10-14) example 85; table A page 1 claim 14	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 October 2005	25/10/2005.

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/021789

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/021789

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